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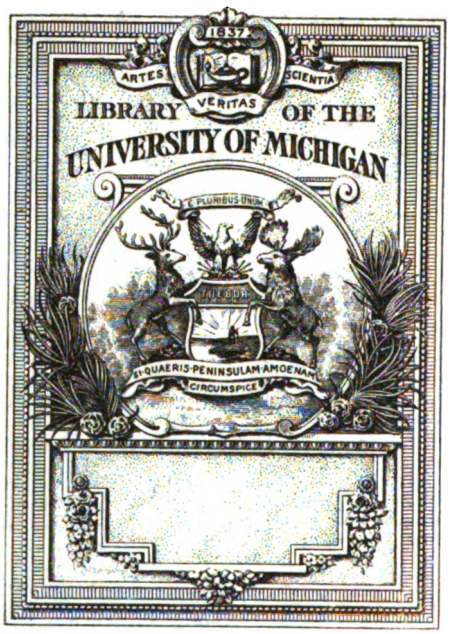

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TRANSACTIONS

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OF THE

PATHOLOGICAL SOCIETY OF LONDON.

VOLUME THE FIFTY-THIRD.

COMPRISING THE REPORT OF THE PROCEEDINGS FOR THE SESSION 1901-1902.

Edited by Samuel G. Shattock.

LONDON:
SMITH, ELDER & CO., 15, WATERLOO PLACE.
1902.

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THE Council think it right to state that the authors of the several communications herein published are alone responsible for the statements made or the views put forward by them.

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Presidents of the Society.

ELECTED	
1846	CHARLES J. B. WILLIAMS, M.D., F.R.S.
1848	CHARLES ASTON KEY.
1850	PETER MERE LATHAM, M.D.
1852	CÆSAR H. HAWKINS, F.R.S.
1853	BENJAMIN GUY BABINGTON, M.D., F.R.S.
1855	JAMES MONCRIEFF ARNOTT, F.R.S.
1857	Sir THOMAS WATSON, Bart., M.D., F.R.S.
1859	Sir WILLIAM FERGUSSON, Bart., F.R.S.
1861	JAMES COPLAND, M.D., F.R.S.
1863	Sir PRESCOTT G. HEWETT, Bart., F.R.S.
1865	THOMAS BEVILL PEACOCK, M.D.
1867.	Sir JOHN SIMON, K.C.B., D.C.L., F.R.S.
1869	Sir RICHARD QUAIN, Bart., M.D., LL.D., F.R.S.
1871	JOHN HILTON, F.R.S.
1873	Sir WILLIAM JENNER, Bart., M.D., G.C.B., D.C.L., F.R.S.
1875	GEORGE D. POLLOCK.
1877	CHARLES MURCHISON, M.D., LL.D., F.R.S.
1879	JONATHAN HUTCHINSON, F.R.S.
1881	Sir SAMUEL WILKS, Bart., M.D., F.R.S.
1883	JOHN WHITAKER HULKE, F.R.S.
1885	JOHN SYER BRISTOWE, M.D., F.R.S.
1887	Sir JAMES PAGET, Bart., D.C.L., LL.D., F.R.S.
1889	WILLIAM HOWSHIP DICKINSON, M.D.
1891	Sir GEORGE MURRAY HUMPHRY, M.D., LL.D., F.R.S.
1893	FREDERICK WILLIAM PAVY, M.D., LL.D., F.R.S.
1895	HENRY TRENTHAM BUTLIN, D.C.L.
1897	JOSEPH FRANK PAYNE, M.D.
1899	WILLIAM WATSON CHEYNE, C.B., F.R.S.
1902	Sir JOHN BURDON SANDERSON, Bart., M.D., D.C.L., F.R.S.

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OFFICERS AND COUNCIL

OF THE

Pathological Society of London,

ELECTED AT

THE GENERAL MEETING, MAY 20TH, 1902,

FOR THE SESSION 1902–1903.

President.

SIR JOHN BURDON SANDERSON, BART., M.D., D.C.L., F.R.S.

Vice-Presidents.

R. J. GODLEE. (1)
W. D. HALLIBURTON, F.R.S. (4)
E. KLEIN, F.R.S. (2)
F. W. PAVY, F.R.S. (3)

Treasurer.

S. COUPLAND.

Council.

Members of Committee of Section A.

R. CRAWFURD.
N DALTON.
J. FAWCETT.
L. FREYBERGER.
S. H. HABERSHON.
T. W. P. LAWRENCE.
G. F. STILL.

Members of Committee of Section B.

F. W. ANDREWES.
W. BULLOCH.
R. T. HEWLETT.
A. MACFADYEN.
J. McFADYEAN.
H. G. PLIMMER.

Members of Committee of Section C.

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E. H. STARLING, F.R.S.

Members of Committee of Section D.

V. HARLEY.
S. G. HÉDIN.
F. G. HOPKINS.

Sectional Secretaries.

Section A.
H. M. FLETCHER.

Section B.
A. G. R. FOULERTON.

Section C.
T. G. BRODIE.

Section D.
A. E. GARROD.

General Secretary and Editor of the 'Transactions.'

S. G. SHATTOCK.

Trustees.

SIR SAMUEL WILKS, BART., F.R.S. J. F. PAYNE. H. MORRIS.

NOTE.—Section A: Pathological Anatomy and Histology. Section B: Bacteriology. Section C: Experimental Pathology. Section D: Chemical Pathology.
(1) Chairman of Section A. (2) Chairman of Section B.
(3) Chairman of Section C. (4) Chairman of Section D.

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Committees.

The members of Council forming each Section (A, Pathological Anatomy and Histology; B, Bacteriology; C, Experimental Pathology; D, Chemical Pathology) constitute committees of reference in the subjects enumerated, with power to add to their numbers in particular cases.

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*** *Members are requested to inform the General Secretary of any change of address, etc., which may be necessary.*

LIST OF MEMBERS OF THE SOCIETY.

Honorary Members.

BOUCHARD, C., M.D., Professor of General Pathology, Paris.
CHAUVEAU, A., M.D., Professor of Physiology at the Medical School of Lyons.
KOCH, R., M.D., Director of the Institute for Infective Diseases, Berlin.
The Right Honourable Lord LISTER, F.R.S., F.R.C.S., 12, Park crescent, Portland place, W.
METCHNIKOFF, E., M.D., Chef de Service à l'Institut Pasteur, Paris.
VON RECKLINGHAUSEN, F. D., Director of the Pathological Institute, Strassburg.
RINDFLEISCH, E., M.D., Professor of Pathological Anatomy in the University of Bonn.
ROUX, P. P. E., M.D., Sous-directeur de l'Institut Pasteur, Paris.
SIMON, SIR JOHN, K.C.B., D.C.L., LL.D., F.R.S., 40, Kensington square, W.
WELCH, W. H., M.D., Professor of Pathology, Johns Hopkins University, Baltimore.
WILKS, SIR SAMUEL, Bart., M.D., LL.D., F.R.S., F.R.C.P., 8, Prince Arthur Road, Hampstead, N.W.
ZIEGLER, E., M.D. Professor of Pathological Anatomy, Freiburg.

EXPLANATION OF ABBREVIATIONS.

P.—President.
T.—Treasurer.
V.-P.—Vice-President.
S.—Secretary.
C.—Member of Council.
E.—Editor of the 'Transactions.'

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GENERAL LIST OF MEMBERS.

Elected

1891 ABBOTT, FRANCIS CHARLES, M.S., 34, Weymouth street, Portland place, W.

1879 **ABERCROMBIE**, JOHN, M.D., 28, Upper Wimpole street, W. (C. 1897-1900.)

1896 ABRAHAMS, BERTRAM LOUIS, B.Sc., M.B., 14, Welbeck street, W.

1883 ACLAND, THEODORE DYKE, M.D., 19, Bryanston square, W. (C. 1892-4.)

1891 ADAMI, J. GEORGE, M.A., M.D., Montreal, Canada.

1890 ADAMS, JAMES, M.D., 4, Chiswick place, Eastbourne.

1848 **AIKIN**, CHARLES A., 12, Ladbroke terrace, W. (C. 1864-6.)

1872 AIKIN, CHARLES EDMUND, 12, Ladbroke terrace, W.

1897 ALCOCK, SAMUEL K., M.D., Portland House, Burslem.

1882 **ALLCHIN**, WILLIAM HENRY, M.D., 5, Chandos street, W.

1884 ANDERSON, ALEXANDER RICHARD, 5, East Circus street, Nottingham.

1897 ANDREWES, FREDERICK W., M.D., Highwood, Hampstead lane, Highgate, N. (C. 1900—. Com. Sect. B, 1901—.)

1902 ARMOUR, DONALD, M.B., 3, Bentinck street mansions, Manchester square, W.

1883 ASHBY, HENRY, M.D., 13, St. John street, Manchester.

1900 AULD, ALEXANDER GUNN, M.D., 23, Henrietta street, Cavendish square, W.

1863 BAGSHAWE, FREDERICK, M.A., M.D., 35, Warrior square, St. Leonard's-on-Sea.

1902 BAINBRIDGE, F. A., M.B., St. Bartholomew's Hospital, E.C.

1856 **Balding**, DANIEL BARLEY, Royston, Herts.

1881 BALLANCE, CHARLES A., M.S., 106, Harley street, W. (C. 1890-2. C. Com. Sect. C, 1901—. S. 1899—1901.)

1875 BARKER, ARTHUR E. J., 87, Harley street, W. (C. 1884-6. V.P. 1896-7.)

1899 BARKER, A. J. G., Kuching, Sarawak, Borneo.

1885 BARLING, GILBERT, M.B., 85, Edmund street, Birmingham. (C. 1894-7.)

1901 BARNARD, HAROLD, M.S., 25, Welbeck street, W.

1874 **BARLOW**, Sir THOMAS, Bart., K.C.V.O., M.D., B.S., 10, Wimpole street, W. (C. 1879-81. V.-P. 1894-6.)

1899 BARRATT, JOHN OGLETHORPE WAKELIN, M.D., 7, Wellington Square, S.W.

1877 BARROW, A. BOYCE, 8, Upper Wimpole street, W.

1881 BARRS, ALFRED GEORGE, M.D., 22, Park place, Leeds.

1853 **BARWELL**, RICHARD, 55, Wimpole street, W. (C. 1862-4. V.-P. 1889-90.)

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1861 **BASTIAN**, H. CHARLTON, M.A., M.D., F.R.S., 8A, Manchester square, W. (C. 1869-71. V.-P. 1885-7.)

1877 BATEMAN, ARTHUR W., B.A., Tenterfield, New South Wales.

1895 BATTEN, FREDERICK E., M.D., 33, Harley street, W.

1876 **BATTESON**, JOHN, 188, Goldhawk road, Shepherd's Bush.

1882 BATTLE, WILLIAM HENRY, 49, Harley street, W. (C. 1898—1901.)

1870 BÄUMLER, CHRISTIAN G. H., M.D., University of Erlangen.

1874 BEACH, FLETCHER, M.B., 79, Wimpole street, W., and Winchester House, Kingston Hill, Surrey.

1892 BEADLES, CECIL F., Colney Hatch Lunatic Asylum, N. (C. 1898—1901.)

1879 BEALE, EDWIN CLIFFORD, M.B., 23, Upper Berkeley street, W.

1852 **BEALE**, LIONEL S., M.B., F.R.S., 61, Grosvenor street, W. (C. 1858-9. V.-P. 1874-5.)

1856 BEALEY, ADAM, M.D., M.A., Felsham Lodge, Hollington park, St. Leonard's-on-Sea.

1900 BEATON, ROBERT MILNE, M.B., 7, Dartmouth park road, N.W.

1897 BEDDARD, ARTHUR P., M.D., 44, Seymour street, W.

1865 BEEBY, WALTER, M.D., Bromley, Kent.

1880 **BEEVOR**, CHARLES EDWARD, M.D., 135, Harley street, W. (C. 1888-90.)

1883 BENHAM, R. FITZROY, 11, Earl's Court square, S.W.

1886 BENNETT, FREDERICK JOSEPH, 17, George street, Hanover square, W.

1877 BENNETT, Sir WILLIAM HENRY, K.C.V.O., 1, Chesterfield street, W. (C. 1891-3.)

1889 BENTLEY, ARTHUR, J. M., M.D., Mena House, Pyramids, Cairo, Egypt.

1878 BERNARD, FRANCIS R., M.D., Prawls, Stone, near Tenterden, Kent.

1882 BERRIDGE, WILLIAM ALFRED, Redhill, Surrey.

1886 BERRY, JAMES, B.S., 21, Wimpole street, W. (C. 1895-7.)

1891 BEVILLE, FREDERICK WELLS, Sussex Lodge, Hillingdon road, Uxbridge, Middlesex.

1856 **Bickersteth**, EDWARD R., 2, Rodney street, Liverpool.

1882 BINDLEY, PHILIP HENRY, M.B., Branksome road, St. Leonard's-on-Sea.

1850 **BIRKETT**, EDMUND LLOYD, M.D., Westbourne Rectory, Emsworth, Hampshire. (C. 1856-7.)

1865 BISSHOPP, JAMES, Mount Pleasant, Tunbridge Wells.

1889 BLACK, ROBERT, M.D., 14, Pavilion Parade, Brighton.

1863 BLANCHET, JEAN B., M.D., M.S., Montreal, Quebec, Canada.

1879 BOILEAU, J. P. H., M.D., Brigade-Surgeon, Army.

1900 BOKENHAM, THOMAS JESSOPP, 10, Devonshire street, Portland place, W.

1900 BOLTON, JOSEPH SHAW, M.D., B.S., B.Sc., The Hall, Claybury, Woodford Bridge, Essex.

1902 BONNEY, W. F. VICTOR, M.D., M.S., 10, Devonshire street, Portland place, W.

1899 BOSANQUET, W. CECIL, M.D., 117*a*, Harley street, W.

1869 BOURNE, WALTER, M.D. (Travelling).

1861 BOWER, RICHARD NORRIS (Travelling).

1881 BOWLBY, ANTHONY A., C.M.G., 24, Manchester square, W. (M.G.C. 1884—1900. C. 1886-8, 1895-7. S. 1893-4. V.-P. 1898—1900.)

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1895 Box, Charles R., M.D., 2, Devonshire place, Portland Place, W.
1892 Boyce, Rubert William, M.S., F.R.S., University College, Liverpool.
1882 Boyd, Stanley, B.S., 134, Harley street, W. (C. 1893-6. V.-P. 1897-9.)
1889 Bradford, John Rose, M.D., F.R.S. 8, Manchester square, W. (C. 1897—1900. C. Com. Sect. C, 1902—. S. 1900-2.)
1880 Bramwell, Byrom, M.D., 23, Drumsheugh Gardens West, Edinburgh.
1889 Bredin, J. Noble, Linden Lodge, Potton, Beds.
1877 Bridges, Robert, M.B., M.A., Manor House, Yattendon, Berks.
1867 **Bridgewater**, Thomas, LL.D. Glas., M.B. Lond., Harrow-on-the-Hill, Middlesex.
1873 Briggs, Jacob Myers, M.D., Coeymans, New York, U.S.A.
1868 Bright, George Charles, M.D., Cannes, Alpes Maritimes, France.
1857 Briscoe, John, 5, Broad street, Oxford.
1885 Briscoe, John F., Westbrooke House, Alton, Hants.
1860 **BROADBENT**, Sir William Henry, Bart., M.D., 84, Brook street, W. (C. 1871-3. V.P. 1882-4.)
1886 Brockatt, Andrew Alexander, M.D., Hazeldean, Malvern.
1884 Brodie, Charles Gordon, Fernhill, Wootton Bridge, Isle of Wight.
1899 Brodie, Thomas Grigor, M.D. (Hon. Secretary, Section C.), 55, Marlborough Mansions, West Hampstead, N.W. (C. 1900—1901. S. Sect. C, 1901—.)
1865 **BROWN**, Augustus, M.D., Dovedale, Wimblehurst road, Horsham, Sussex.
1871 Brown, Frederick Gordon, 17, Finsbury circus, E.C.
1866 **BROWNE**, Lennox, 15, Mansfield street, W.
1877 Bruce, J. Mitchell, M.D., 23, Harley street, W.
1890 Brunton, Sir T. Lauder, M.D., D.Sc., LL.D., F.R.S., 10, Stratford place, W.
1898 Bryant, John Henry, M.D., 4, St. Thomas's street, London bridge, S.E.
1855 **BRYANT**, Thomas, M.Ch., 27, Grosvenor street, Grosvenor square. (C. 1863-6. V.-P. 1877-9.)
1894 Buchanan, George Seaton, M.D., 9, Hammersmith terrace, W.
1890 Buckland, Francis O., M.A., M.B., C.M., Brockenhurst, Hants.
1899 Bulloch, William, M.D., M.B., C.M., 3, New Inn, Wych Street, Strand, W.C. (C. Com. Sect. B, 1901—.)
1891 Burghard, Frédéric François, M.D., M.S., 86, Harley street, W.
1880 Burton, Samuel Herbert, M.B., 50, St. Giles' street, Norwich.
1900 Busch, Joseph Paul-Zum, M.D., Chiswell House, 133, Finsbury Pavement, E.C.
1872 **BUTLIN**, Henry Trentham, D.C.L., 82, Harley street, W. (M.G.C. 1875-86. C. 1876-8, 1887-9. S. 1884-6. V.-P. 1891-2. P. 1895-7.)
1883 **BUXTON**, Dudley W., M.D., 82, Mortimer street, W.
1856 **BUZZARD**, Thomas, M.D., 74, Grosvenor street, W. (C. 1869-70. V.-P. 1881-3.)

1901 Caddy, Adrian, M.B., St. George's Hospital, S.W.
1899 Caddy, Arnold, 2/2, Harington street, Calcutta.

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1893 CALEY, HENRY ALBERT, M.D., 24, Upper Berkeley street, W.

1897 CALVERT, JAMES, M.D., The Warden's House, St. Bartholomew's Hospital, E.C.

1892 CAMPBELL, HENRY JOHNSTONE, M.D., 36, Manningham lane, Bradford.

1891 CARLESS, ALBERT, M.S., 10, Welbeck street, W.

1891 CARR, JOHN WALTER, M.D., 19, Cavendish place, W.

1897 **Carwardine**, THOMAS, M.S., 16, Victoria square, Clifton, Bristol.

1877 CASSON, JOHN HORNSBY, H.B.M. Legation, Teheran, Persia.

1899 CAUTLEY, EDMUND, M.D., 15, Upper Brook street, W.

1864 CAY, CHARLES VIDLER, Deputy Surgeon General, 25, Newton place, Glasgow.

1863 CAYLEY, WILLIAM, M.D., 27, Wimpole street, W. (M.G.C. 1869-84. C. 1870-1, 1875-8. S. 1872-4. V.-P. 1884-6. T. 1888-93.)

1869 CHAFFERS, EDWARD, Keighley, Yorkshire.

1891 CHAPLIN, ARNOLD, M.D., 41, Finsbury square, E.C.

1884 CHAVASSE, THOMAS FREDERICK, M.D., C.M., 22, Temple row, Birmingham.

1901 CHEATLE, G. LENTHAL, 117, Harley Street, W.

1879 CHEYNE, WILLIAM WATSON, C.B., M.B., C.M., F.R.S., 75, Harley street, W. C. 1885-7. (M.G.C. 1890-6. V.-P. 1892-3. P. 1899—1902.)

1902 CHILDS, CHRISTOHER, M.D., D.P.H., 10, Manchester square, W.

1873 CHISHOLM, EDWIN, M.D., 44, Rosslyn gardens, Darlinghurst, near Sydney, New South Wales [care of Messrs. Dawson, 121, Cannon street, E.C.].

1865 **CHURCH**, Sir WILLIAM SELBY, Bart., K.C.B., P.R.C.P., 130, Harley street, W. (M.G.C. 1869-74. C. 1871-3. V.-P. 1894-6.)

1868 **CHURCHILL**, FREDERICK, M.D., 4, Cranley gardens, Queen's gate S.W.

1898 CHURTON, THOMAS, M.D., 35, Park square, Leeds.

1861 **CLAPTON**, EDWARD, M.D., Towercroft, 41, Eltham road, Lee, S.E.

1872 CLARK, ANDREW, 71, Harley street, W.

1886 CLARK, FRANCIS WILLIAM, M.B., Victoria, Hong Kong.

1885 CLARKE, JOHN MICHELL, M.D., 28, Pembroke road, Clifton, Bristol.

1881 CLARKE, W. BRUCE, M.B., 51, Harley street, W. (C. 1892-4.)

1899 CLEVELAND, ARTHUR JOHN, M.D., 45, Shooter's Hill road, Blackheath park, S.E.

1875 **CLUTTON**, HENRY HUGH, M.A., 2, Portland place, W. (C. 1884-6. M.G.C. 1889-94. V.-P. 1892-3.)

1865 **Coates**, CHARLES, M.D., 10, Circus, Bath.

1892 COLE, ROBERT HENRY, M.D., Moorcroft, Hillingdon, Uxbridge.

1886 COLLIER, WILLIAM, M.D., High street, Oxford.

1888 COLLINS, Sir WILLIAM JOB, M.D., M.S., 1, Albert terrace, Regent's park, N.W.

1878 COLLYNS, R. T. POOLE, Kingsley, Lingfield road, Wimbledon.

1888 COLMAN, WALTER STACY, M.D., 22, Wimpole street, W.

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1882 COLQUHOUN, DANIEL, M.D., Dunedin, New Zealand.
1896 CONNELL, W. T., M.D., Kingston, Canada.
1891 COOK, HERBERT G. GRAHAM, M.D., 22, Newport road, Cardiff.
1858 COOKE, R. T. E. BARRINGTON, 15, St. Nicholas cliff, Scarborough, Yorkshire.
1866 COOMBS, ROWLAND HILL, M.D., Mill street, Bedford.
1892 COOPER, C. DUDLEY,
1900 CORNER, EDRED MOSS, M.B., St. Thomas's Hospital, S.E.
1899 CORNER, HARRY, M.D., Brook House, Southgate, N.
1876 COTTLE, WYNDHAM, M.D., 39, Hertford street, W.
1861 **COUPER**, JOHN, 80, Grosvenor street, W. (C. 1870-2.)
1873 **COUPLAND**, SIDNEY, M.D. (TREASURER), 16, Queen Anne street, W. (M.G.C. 1882-6. C. 1878-81, 1889-91. S. 1886-8. V.-P. 1892-3. T. 1894—.)
1897 CRAWFURD, RAYMOND H. P., M.D., 71, Harley street, W. (C. Com. Sect. A, 1902—.)
1884 CRICHTON, GEORGE, M.D., 96, Earl's Court road, W.
1873 CRIPPS, WILLIAM HARRISON, 2, Stratford place, W. (C. 1883-5. V.-P. 1893-4.)
1877 **CROCKER**, HENRY RADCLIFFE, M.D., 121, Harley street, W. (C. 1887-9. V.-P. 1897-9.)
1886 CROOKSHANK, EDGAR, M.B., Saint Hill, East Grinstead, Sussex. (C. 1890-3. V.-P., 1900-2.)
1875 CROSS, FRANCIS RICHARDSON, 5, The Mall, Clifton, Bristol.
1890 CROWLE, THOMAS H. RICKARD, 35, St. James's place, S.W.
1889 CUFF, ROBERT, M.B., 1, The Crescent, Scarborough.
1885 CULLINGWORTH, CHARLES JAMES, M.D., 14, Manchester square, W.
1871 CUMBERBATCH, A. ELKIN, 80, Portland place, W.
1893 CURTIS, HENRY JONES, M.D., 15, Harley street, W.

1884 DAKIN, W. RADFORD, M.D., B.S., 8A, Grosvenor street, Grosvenor square, W.
1883 DALTON, NORMAN, M.D., 4, Mansfield street, W. (C. Com. Sect. A, 1901—.)
1873 DAVIDSON, ALEXANDER, M.D., 2, Gambier terrace, Liverpool.
1883 DAVIS, EDWIN HARRY, West Hartlepool.
1859 **Davis**, FRANCIS WILLIAM, R.N.
1879 DAVY, HENRY, M.D., 29, Southernhay, Exeter.
1894 DAWSON, BERTRAND, M.D., 110, Harley street, W.
1899 DEAN, GEORGE, M.D., The Jenner Institute of Preventive Medicine, Queensberry Lodge, Aldenham, Herts.
1889 DEAN, HENRY PERCY, M.B., M.S., 69, Harley street, W. (C. 1900—1901.)
1899 DE CHAZAL, EDMOND LUCIEN, M.D., Port Louis, Mauritius.
1887 DELÉPINE, SHERIDAN, M.B., C.M., Owens College, Manchester. (C. 1899—1901.)
1880 DENT, CLINTON T., 61, Brook street, W.

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Elected

1871 DICKINSON, EDWARD HARRIMAN, M.A., M.D., 51A, Rodney street, Liverpool.

1858 **DICKINSON**, WILLIAM HOWSHIP, M.D., 9, Chesterfield street, W. (C. 1866-8. S. 1869-71. V.-P. 1872-4. P. 1889-90.)

1890 **DICKINSON**, WILLIAM LER, M.D., 9, Chesterfield street, W.

1900 DIXON, W. E., M.D., 28, Benson road, Forest hill, S.E.

1872 DIVER, EBENEZER, M.D., Garstone, St. Margaret's-on-Thames, Twickenham.

1872 DORAN, ALBAN HENRY GRIFFITHS, 9, Granville place, W. (C. 1882-4. V.-P. 1894-6.)

1893 DOWSON, WALTER, M.D., 46, Alleyn road, West Dulwich.

1877 DRAKE-BROCKMAN, EDWARD F., 14, Welbeck street, W.

1880 DRESCHFELD, JULIUS, M.D., 3, St. Peter's square, Manchester. (C. 1896-9.)

1896 DREW, DOUGLAS, M.B., 49, Devonshire street, Portland place, W.

1893 DRYSDALE, JOHN HANNAH, M.D., 11, Devonshire place, W.

1865 **DUCKWORTH**, Sir DYCE, M.D., LL.D., 11, Grafton street, Bond street, W. (C. 1877.)

1847 **DUDGEON**, ROBERT E., M.D., 22, Carlton hill, St. John's Wood, N.W.

1902 DUDGEON, L. S., 6, Powis gardens, Bayswater, W.

1871 DUKES, CLEMENT, M.D., B.S., Sunnyside, Rugby.

1877 DUNBAR, J. J. MACWHIRTER, M.D., Hedingham House, Clapham common, S.W.

1877 DUNCAN, ANDREW, M.D., 24, Chester street, Grosvenor place, S.W.

1889 DUNCAN, JOHN, M.D., St. Petersburg.

1884 DUNN, LOUIS ALBERT, M.B., M.S., 51, Devonshire street, Portland place, W.

1879 DURHAM, FREDERIC, M.B., 52, Brook street, W.

1899 EASTES, GEORGE LESLIE, M.B., B.Sc., 35, Gloucester terrace, W.

1901 EASTWOOD, A., M.B., 175, Amesbury avenue, Streatham hill, S.W.

1893 ECCLES, WILLIAM MCADAM, M.S., 124, Harley street, W.

1892 EDDOWES, ALFRED, M.D., 28, Wimpole street, W.

1880 **EDMUNDS**, WALTER, M.C., 2, Devonshire place, Portland place, W. (C. 1892-4. C. Com. Sect. C, 1901-2.)

1882 EDWARDS, F. SWINFORD, 55, Harley street, W.

1889 ELAM, WILLIAM HENRY, New Barnet, Herts.

1883 ELDER, GEORGE, M.D., 17, Regent street, Nottingham.

1867 ELLIS, JAMES, M.D., Coburg street, Fratton, Portsmouth, and California.

1902 EMANUEL, JOSEPH GEORGE, M.B., B.S., B.Sc., General Hospital, Birmingham.

1863 ENGELMANN, GEORGE JULIUS, M.D., A.M., 336, Beacon street, Boston, Mass., U.S.A.

1875 EVANS, JULIAN AUGUSTUS, A.M., M.D., 123, Finborough road, Redcliffe square, S.W.

1894 EVANS, WILLMOTT H., M.D., B.S., B.Sc., 2, Upper Wimpole street, W.

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Elected

1879 EVE, FREDERIC S., 125, Harley street, W. (M.G.C. 1884-94. C. 1885-7. V.-P. 1895-7.)

1876 EWART, JAMES COSSAR, M.B., C.M., F.R.S., School of Medicine, Edinburgh.

1881 EWART, Sir JOSEPH, M.D., Bewcastle, Dyke road, Brighton.

1877 **EWART**, WILLIAM, M.D., 33, Curzon street, W. (C. 1889-91.)

1859 **Ewens**, JOHN, 17, Redland Grove, Bristol.

1887 EYLES, CHARLES HENRY, Gold Coast Colony.

1897 EYRE, JOHN W. H., M.D., Embankment Chambers, Villiers street, W.C.

1889 FAIRBANK, FREDERICK ROYSTON, M.D., Hillside, Westcott, Dorking.

1894 FAWCETT, JOHN, M.D., 26, St. Thomas's street, S.E. (C. Com. Sect. A, 1902—.)

1872 FENN, EDWARD L., M.D., Grey Friars, Colchester.

1902 FENNELL, CHARLES HENRY, M.A., M.B., 10, Devonshire street, Portland place, W.

1883 FENWICK, E. HURRY, 14, Savile row, W. (C. 1894-7.)

1872 FENWICK, JOHN C. J., M.D., Long Framlington, Morpeth.

1863 **FENWICK** SAMUEL, M.D., 29, Harley street, W.

1892 FENWICK, W. SOLTAU, M.D., 8, Devonshire street, W.

1885 FÉRÉ, CHARLES, M.D., Médecin de Bicêtre; Boulevard St. Michel 37, Paris.

1897 FISHER, THEODORE, M.D., 25, Pembroke road, Clifton, Bristol.

1893 FLETCHER, H. MORLEY, M.A., M.D., B.C., (HON. SECRETARY, SECT. A), 98, Harley street, W. (S. Sect. A, 1901—.)

1872 FORBES, DANIEL MACKAY, 32, Oakfield road, West Croydon.

1866 **Foster**, Sir BALTHAZAR WALTER, M.D., M.P., 30, Grosvenor road, Westminster.

1872 FOTHERBY, HENRY I., M.D., Woodthorpe Cote, Reigate.

1891 FOULERTON, ALEXANDER GRANT RUSSELL (HON. SECRETARY, SECT. B), Middlesex Hospital, W. (C. 1900—1901. S. Sect. B, 1901—.)

1880 FOWLER, JAMES KINGSTON, M.A., M.D., 35, Clarges street, W. (C. 1887-8.)

1878 FOX, THOMAS COLCOTT, B.A., M.B., 14, Harley street, W. (C. 1892-4.)

1902 FREMLIN, H. STUART, Government Lymph Laboratory, Chelsea Bridge, S.W.

1896 FREYBERGER, LUDWIG, M.D., 41, Regent's park road, N.W. (C. Com. Sect. A, 1902—.)

1891 FRIPP, ALFRED DOWNING, C.B., M.V.O., M.S., 19, Portland place, W.

1864 FRODSHAM, JOHN MILL, M.D., Streatham, S.W.

1899 FÜRTH, KARL, M.D., 94, Harley street, W.

1894 FURNIVALL, PERCY, 28, Weymouth street, Portland place, W.

1893 FYFFE, WILLIAM KINGTON, M.B., 1, Boullcott street, Wellington, New Zealand.

1880 GABBETT, HENRY SINGER, M.D., 8, Chiswick place, Eastbourne.

1858 **Gairdner**, Sir WILLIAM TENNANT, K.C.B., M.D., LL.D.Edin., F.R.S., 32, George square, Edinburgh. (V.-P. 1891-2.)

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Elected

1890 Galloway, James, M.A., M.D., 54, Harley street, W. (C. 1899-1902. Com. Sect. A, 1901-2.)

1870 Galton, John H., M.D., Sylvan road, Upper Norwood, S.E.

1846 **GARROD**, Sir Alfred Baring, M.D., F.R.S., 10, Harley street, W. (C. 1851. V.-P. 1863-5.)

1892 Garrod, Archibald Edward, M.D. (Hon. Secretary, Sect. D), 9, Chandos street, Cavendish square, W. (C. 1898—1901. S. Sect. D, 1901—.)

1879 Garstang, Thomas Walter Harropp, Englefield, Delamer road, Bowdon.

1872 Garton, William, M.D., Inglewood, Aughton, near Ormskirk, Lancashire.

1902 Gask, G. E., M.B., St. Bartholomew's Hospital, E.C.

1880 Gibbes, Heneage, M.B., University of Michigan, Ann Arbor, Michigan, U.S.A.

1853 **GIBBON**, Septimus, M.D., 39, Oxford terrace, Hyde park, W.

1878 Gibbons, Robert A., M.D., 29, Cadogan place, S.W.

1893 Gibbs, Charles, 115, Harley street, W.

1872 Gilbart-Smith, Thomas, M.D., 68, Harley street, W.

1876 Gill, John, M.D., 30, West mall, Clifton, Bristol.

1881 Glynn, Thomas Robinson, M.D., 62, Rodney street, Liverpool.

1898 Goadby, Kenneth Weldon, The Mall, Wanstead, Essex.

1873 Godlee, Rickman John, M.B., M.S., 19, Wimpole street, W. (M.G.C. 1875-84. C. 1877-80, 1891-2. S. 1887-9. V.-P. 1893-4, 1902—. Chairman, Sect. A.)

1878 Golding-Bird, Cuthbert H., M.B., B.S., 12, Queen Anne street, W. (C. 1885-7. V.-P. 1894-6.)

1890 Goodall, E. Wilberforce, M.D., The Eastern Hospital, Homerton, N.E.

1902 Goodbody, Francis Woodcock, M.D., 6, Chandos street, W.

1871 Goodhart, James Frederic, M.D., 25, Portland place, W. (M.G.C. 1874-86. C. 1876-8, 1886-8. S. 1883-5. V.-P. 1892-3.)

1894 Gossage, Alfred Milne, M.B., B.Ch., 54, Upper Berkeley street, W.

1875 Gould, Alfred Pearce, M.S., 10, Queen Anne street, W. (C. 1883-5. V.-P. 1898-1900.)

1870 Gowers, Sir William, M.D., F.R.S., 50, Queen Anne street, W. (C. 1878-9. V.P. 1896-7.)

1888 Grant, J. Dundas, M.A., M.D., C.M., 18, Cavendish square, W.

1900 Green, Alan B., M.A., M.D., B.C., 31, Cheyne court, Chelsea, S.W.

1895 Green, Charles David, M.D., The Ferns, South street, Romford. (C. 1900-2. Com. Sect. A, 1901-2.)

1867 Green, T. Henry, M.D., 74, Wimpole street, W. (M.G.C. 1869-83. C. 1871-3, 1878-9. S. 1875-6. V.-P. 1886-8.)

1873 Greenfield, William Smith, M.D., B.S., 7, Heriot row, Edinburgh. (M.G.C. 1874-81. C. 1877-80. V.-P. 1893-4.)

1886 Greves, Edwin Hyla, M.D., Rodney House, Suffolk road, Bournemouth.

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Elected

1887 GRIFFITHS, JOSEPH, M.D., C.M., 63, Trumpington street, Cambridge.
1876 GRIFFITHS, THOMAS D., M.D., Hearne Lodge, Swansea.
1900 GRUBE, KARL, M.D., Neuenahr, Germany.
1899 GRUBER, R., M.D., 67, Wimpole street, W.
1902 GRÜNBAUM, O. F. F., M.B., B.C., 45, Ladbroke grove, W.

1887 HABERSHON, SAMUEL HERBERT, M.D., 88, Harley street, W. (C. Com. Sect. A, 1902—.)
1851 **HACON**, E. DENNIS, 269, Mare street, Hackney, N.E. (C. 1872.)
1892 HADLEY, WILFRED JAMES, M.D., 58, Harley street, W.
1882 HAIG, ALEXANDER, M.D., 7, Brook street, W.
1899 HALL, ARTHUR J., M.B., 342, Glossop road, Sheffield.
1901 HALLIBURTON, WILLIAM DOBINSON, M.D., F.R.S., Church Cottage, 17, Marylebone road, W. (V.-P., Chairman Sect. D.)
1894 HALLIDIE, ANDREW HALLIDIE SMITH, M.B., 50, Noord street, Johannesburg.
1886 HAMILTON, DAVID JAMES, M.B., 41, Queen's road, Aberdeen.
1890 HANDFIELD-JONES, MONTAGU, M.D., 35, Cavendish square, W.
1886 HANDFORD, HENRY, M.D., 6, Regent street, Nottingham.
1902 HANDLEY, WILLIAM SAMPSON, M.S., M.D., 41, Devonshire street, W.
1891 HANKIN, E. H., Agra, India.
1882 HARBINSON, ALEXANDER, M.D., County Lunatic Asylum, Lancaster.
1893 HARLEY, VAUGHAN, M.D., 25, Harley street, W. (C. Com. Sect. D, 1901—.)
1902 HARMAN, NATHANIEL BISHOP, B.A., M.B., Middlesex Hospital, W.
1901 HARMER, W. D., 45, Weymouth street, W.
1879 HARRIS, VINCENT DORMER, M.D., 22, Queen Anne street, W.
1891 HASLAM, WILLIAM F., 54, Newhall street, Birmingham.
1899 HAWKES, CLAUDE SOMERVILLE, Glencairn, Wickham terrace, Brisbane, Queensland, Australia.
1886 HAWKINS, FRANCIS HENRY, M.D., 73, London street, Reading.
1890 HAWKINS, HERBERT PENNELL, M.D., 56, Portland place, W. (C. 1898—1901.)
1856 **HEATH**, CHRISTOPHER, 36, Cavendish square, W. (C. 1866-7. V.-P. 1879-81.)
1900 HEATON, CHARLES, Westgate-on-Sea, Thanet, Kent.
1892 HEATON, GEORGE, M.B., B.Ch., 33, Temple row, Birmingham.
1881 HEBB, RICHARD G., M.A., M.D., 9, Suffolk street, S.W. (M.G.C. 1891—1900. C. 1891-3. 1898—1901. S. 1896-7.)
1884 HEBBERT, CHARLES ALFRED, care of C. Baylor, 7, Water street, Boston, U.S.A.
1901 HÉDIN, SVEN GUSTAV, M.D., Jenner Institute of Preventive Medicine, Chelsea bridge, S.W. (C. Com. Sect. D, 1901—.)
1879 HENDERSON, GEORGE COURTENAY, M.D., Kingston, Jamaica, West Indies.
1869 HENSLEY, PHILIP J., M.D., 4, Henrietta street, W.
1884 HERRINGHAM, WILMOT PARKER, M.D., 40, Wimpole street, W. (C. 1894-7.)

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1892 HEWLETT, RICHARD TANNER, M.D., Lyddon House, Avenue road, Southfields, S.W. (C. Com. Sect. B, 1902—.)

1897 HICHENS, PEVERELL S., M.B., B.Ch., 45, Sheep street, Northampton.

1900 HILLIER, WILLIAM THOMAS, Rougemont, Beaconsfield road, St. Albans.

1880 HOBSON, JOHN MORRISON, M.D., Glendalough, Morland road, Croydon.

1854 **HOLMES**, TIMOTHY, 6, Sussex place, Hyde park, W. (C. 1862-3. S. 1864-7. C. 1868. V.-P. 1869-71.)

1878 HOOD, DONALD WILLIAM CHARLES, M.D., 43, Green street, Park lane, W.

1864 HOOD, WHARTON P., M.D., 11, Seymour street, W.

1895 HOPKINS, FREDERICK GOWLAND, M.B., New Museums, Cambridge. (C. 1899—. Com. Sect. D, 1901.)

1900 HORDER, THOMAS J., M.D., B.Sc., 141, Harley street, W.

1897 HORNE, WALTER J., M.B., 27, New Cavendish street, Portland place, W.

1883 HORSLEY, Sir VICTOR, M.B., B.S., F.R.S., 25, Cavendish square, W. (C. 1888-9. V.-P. 1900-1902.)

1896 HORTON-SMITH, PERCIVAL, M.D., B.C., 15, Upper Brook street, W.

1880 **HOVELL**, T. MARK, 105, Harley street, W.

1893 HOWARD, ROBERT JARED BLISS, M.D., 31, Queen Anne street, W.

1875 HOWSE, Sir HENRY GREENWAY, M.S., 59, Brook street, W. (M.G.C. 1876-84. C. 1878-81.)

1856 **HUDSON**, JOHN, M.D., 11, Cork street, W.

1874 HUMPHREYS, HENRY, M.D., St. Mary Church road, Torquay.

1897 HUNT, E. L., c/o King, King, and Co., Bombay.

1897 HUNT, GEORGE B., M.D., 47, Albemarle crescent, Scarborough.

1888 HUNTER, WILLIAM, M.D., 103, Harley street, W. (C. 1897-1900.)

1852 **HUTCHINSON**, JONATHAN, F.R.S., 15, Cavendish square, W. (C. 1856-9. V.-P. 1872-3, 1881-3. P. 1879-80.)

1901 HUTCHISON, ROBERT, M.D., 22, Queen Anne street, W.

1884 HUTTON, HENRY RICHMOND, M.B., 8A, St. John street, Manchester.

1880 INGRAM, ERNEST FORTESCUE, Newcastle, Natal, S. Africa.

1886 JACKSON, ARTHUR MOLYNEUX, M.D., Kent County Asylum, Barming Heath, Maidstone.

1865 JACKSON, J. HUGHLINGS, M.D., F.R.S., 3, Manchester square, W. (C. 1872-3. V.-P. 1888-9.)

1875 JALLAND, WILLIAM HAMERTON, St. Leonard's House, Museum street, York.

1897 JAMES, GEORGE T. B., Carlisle mansions, Victoria street, S.W.

1888 JAMES, JAMES THOMAS, M.D., 30, Harley street, W.

1853 **Jardine**, JOHN LEE, Braydell Lodge, Wivelsfield, near Haywards Heath.

1897 **JENNER**, LOUIS, M.B., 4A, Bloomsbury square, W.C.

1881 JENNINGS, WILLIAM OSCAR, M.D., 74, Avenue Marceau, Paris.

1866 JESSOP, THOMAS RICHARD, 31, Park square, Leeds.

1878 JOHNSON, ARTHUR JUKES, Yorkville, Ontario, Canada.

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1876 JOHNSON, CHARLES HENRY, Winton House, Basingstoke, Hants.

1901 JOHNSON, EDWARD ANGAS, M.B., B.S., St. Catharine's Prospect, South Australia.

1888 JOHNSON, RAYMOND, M.B., B.S., 11, Wimpole street, Cavendish square, W. (C. 1896-9.)

1899 JONAS, HERBERT C., Duxford, Cambridgeshire.

1853 **JONES**, SYDNEY, M.B., 8A, New Cavendish street, W. (C. 1864-6. V.-P. 1886-7.)

1888 JONES, TALFOURD, M.B., St. Davids, 1, Lascelles terrace, Eastbourne.

1862 **JONES**, THOMAS RIDGE, M.D., 4, Chesham place, S.W. (C. 1882-4.)

1886 JULER, HENRY EDWARD, 23, Cavendish square, W.

1898 KEEP, ARTHUR CORRIE, M.D., M.C., 14, Gloucester place, W.

1867 KELLY, CHARLES, M.D., Ellesmere, Gratwicke road, Worthing, Sussex (M.G.C. 1872-4. C. 1874.)

1897 KELLY, CHARLES E. M., M.D., Witney, Oxon.

1901 KELYNACK, T. N., M.D., 53, Harley street, W.

1879 KESTEVEN, WILLIAM HENRY, 118, Stamford street, S.E.

1859 KIALLMARK, HENRY WALTER, 5, Pembridge gardens, W. (C. 1875-6.)

1882 KIDD, PERCY, M.D., 60, Brook street, W. (C. 1889-91.)

1871 KING, ROBERT, M.B., Boyfield House, Moulton, Spalding, Lincolnshire.

1852 **KINGDON**, J. ABERNETHY, Threadneedle street, E.C.

1901 KLEIN, EDWARD EMANUEL, M.D., F.R.S., Harewood, Riversdale gardens, Twickenham Park, Twickenham. (V.-P., Chairman, Sect. B, 1901—.)

1902 KOENIG, RENÉ PAUL, M.D., 42, Welbeck street, W.

1888 KYNSEY, Sir WILLIAM RAYMOND, K.C.M.G., Oriental Club, Hanover square, W. [Travelling.]

1878 LANCEREAUX, ETIENNE, M.D., 44, Rue de la Bienfaisance, Paris.

1882 LANE, WILLIAM ARBUTHNOT, M.B., M.S., 21, Cavendish square, W. (C. 1891-3.)

1869 LARCHER, O., M.D.Par., 97, Rue de Passy, Paris. [M. Kliensieck, Libraire, Rue de Lille 11, Paris, per Messrs. Longmans.]

1884 LARDER, HERBERT, Whitechapel Infirmary, Vallance road, N.E.

1897 LATHAM, ARTHUR C., M.D., 44, Brook street, W.

1873 LATHAM, PETER WALLWORK, M.D., 17, Trumpington street, Cambridge.

1876 LAW, WILLIAM THOMAS, M.D., 32, Weymouth street, Portland place, W.

1853 LAWRENCE, HENRY JOHN HUGHES, Picton House, Llandowror, St. Clears. (C. 1873-5.)

1892 LAWRENCE, THOMAS WILLIAM PELHAM, M.B., 12, Bisham gardens, Highgate, N. (C. Com. Sect. A, 1901—.)

1893 LAWSON, ARNOLD, M.D., 12, Harley street, W.

1859 LAWSON, GEORGE, 12, Harley street, W. (C. 1870-1. V.-P. 1884-5.)

1879 LAYCOCK, GEORGE LOCKWOOD, M.B., Melbourne, Victoria, Australia.

1891 LAZARUS-BARLOW, WALTER SYDNEY, M.D., Cecil House, Cavendish road, Sutton, Surrey. (C. Com. Sect. C, 1901—.)

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1901 LEATHES, JOHN BERESFORD, M.B., 10, Park mansions, Battersea park, S.W.
1875 LEDIARD, HENRY AMBROSE, M.D., 35, Lowther street, Carlisle. (C. 1897-1900.)
1877 **LEES**, DAVID B., M.D., 22, Weymouth street, W. (C. 1890-2.)
1867 LEES, JOSEPH, M.D., 21, Brixton road, S.W.
1877 LEESON, JOHN RUDD, M.D., C.M., 6, Clifden road, Twickenham.
1868 LEGG, JOHN WICKHAM, M.D. (Travelling.) (C. 1874-5.)
1902 LEGG, THOMAS PERCY, M.B., 141, Harley street, W.
1892 LEITH, ROBERT FRASER CALDIE, M.B., C.M., B.Sc.
1892 **Leudet**, ROBERT, 16, Rue du Contrat Social, Rouen, France.
1897 LISTER, THOMAS DAVID, 50, Brook street, W.
1895 LITTLE, ERNEST GRAHAM GORDON, M.D., 61, Wimpole street, W.
1889 LITTLE, JOHN FLETCHER, M.B., 32, Harley street, W.
1863 **LITTLE**, LOUIS S., 31, Grosvenor street, W.
1896 LITTLEWOOD, HARRY, 25, Park square, Leeds.
1874 LIVEING, EDWARD, M.D., 52, Queen Anne street, W.
1863 **LIVEING**, ROBERT, M.D., 11, Manchester square, W. (C. 1876.)
1881 LUBBOCK, MONTAGU, M.D., 19, Grosvenor street, W.
1897 LUCAS, ALBERT, 9, Easy row, Birmingham.
1873 LUCAS, R. CLEMENT, M.B., B.S., 50, Wimpole street, W. (C. 1883-5.)
1879 LUNN, JOHN REUBEN, St. Marylebone Infirmary; Rackham street, Ladbroke grove road, W. (C. 1897-1900.)
1887 LYON, THOMAS GLOVER, M.D., 1, Victoria square, S.W.

1893 MCFADYEAN, JOHN, M.B., Royal Veterinary College, Great College street, N.W. (C. 1899—. Com. Sect. B, 1901—.)
1896 MACFADYEN, ALLAN, M.D., B.Sc., Jenner Institute of Preventive Medicine, Chelsea gardens, S.W. (C. 1900—. Com. Sect. B, 1901—.)
1899 MCGAVIN, LAWRIE H., 21, Montague street, Portman square, W.
1882 MACKENZIE, FREDERIC MORELL, 29, Hans place, S.W.
1885 MACKENZIE, HECTOR WILLIAM GAVIN, M.A., M.D., 34, Upper Brook street, Grosvenor square, W. (C. 1895-7.)
1870 MACKENZIE, JOHN T., Bombay, India.
1878 MACKENZIE, STEPHEN, M.D., Merrycourt, Great Bookham, Leatherhead, Surrey. (C. 1888-90.)
1902 MACKIE, FREDERIC PERCIVAL, Fylton Rectory, Gloucestershire.
1879 MACLAGAN, THOMAS JOHN, M.D., 9, Cadogan place, S.W.
1865 MACLAURIN, HENRY NORMAND, M.D., 187, Macquarie street, Sydney, New South Wales.
1896 MCWEENEY, EDMOND JOSEPH, M.D., M.Ch., 84, St. Stephen's green, Dublin.
1885 MAGUIRE, ROBERT, M.D., 4, Seymour street, W.
1877 MAKINS, GEORGE HENRY, C.B., 47, Charles street, Berkeley square, W. (C. 1889-91. V.-P. 1899-1901.)
1887 MALCOLM, JOHN DAVID, M.B., C.M., 13, Portman street, W.
1892 MANN, HAROLD EDWARD, Alderney.

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1890 MANSON, PATRICK, C.M.G, M.D., C.M., F.R.S., 21, Queen Anne street, W. (C. 1900-1.)

1876 MAPLES, REGINALD, Kingsclere, near Newbury.

1868 MARSH, F. HOWARD, 30, Bruton street, W. (C. 1876-7.) (V.-P. 1889-90.)

1887 MARTIN, SIDNEY, M.D., B.S., F.R.S., 10, Mansfield street, W. (C. 1893-6. V.-P. 1900-1902.)

1889 MASON, DAVID JAMES, M.D., Rosemont, Maidenhead.

1867 MASON, PHILIP BROOKES, Burton-on-Trent.

1898 MASTERMAN, ERNEST WILLIAM GURNEY, 3, Newnham terrace, Cambridge.

1892 MASTERS, JOHN ALFRED, M.D., 31, Albert Gate, Hyde Park, S.W.

1884 MAUDSLEY, HENRY CARR, M.D., 11, Spring street, Melbourne, Victoria.

1897 MAXWELL, J. P., c/o E.P. Mission, Amoy, China.

1900 MAXWELL, JAMES LAIDLAW, M.D., E.P. Mission, Yai-nan-fu, Formosa, *vid* Hong Kong.

1852 **MAY**, GEORGE, M.B., Reading.

1888 MAY, WILLIAM PAGE, M.D., B.Sc., 9, Manchester square, W., and Helouan, near Cairo, Egypt (November to April).

1881 MAYLARD, ALFRED ERNEST, M.B., 4, Berkeley terrace, Glasgow.

1874 MEREDITH, WILLIAM APPLETON, C.M., 21, Manchester square, W.

1894 MICHELS, ERNST, M.D., 48, Finsbury square, E.C.

1900 MILBURN, LESLIE, Hollywood House, Wimbledon common, S.W.

1882 MONEY, ANGEL, M.D., Hunter street, Sydney, New South Wales.

1901 MOORE, ALFRED, Reculver Villa, Cheam road, Sutton, Surrey.

1899 MOORE, FREDERICK CRAVEN, M.D., The Priory, Ardwick Green, Manchester.

1879 MOORE, NORMAN, M.D., 94, Gloucester place, Portman square, W. (C. 1885-7. M.G.C. 1889-1900. V.-P. 1895-7.)

1875 MORGAN, JOHN H., 68, Grosvenor street, W. (C. 1886-8.)

1874 MORISON, ALEXANDER, M.D., C.M., 14, Upper Berkeley street, W.

1869 **MORRIS**, HENRY, M.A., M.B. (TRUSTEE), 8, Cavendish square, W. (C. 1877-9, 1884-6. S. 1881-3. V.-P. 1888-9.)

1879 MORRIS, MALCOLM ALEXANDER, 8, Harley street, W.

1894 MORRICE, GEORGE GAVIN, M.D., Holy Trinity Vicarage, Weymouth.

1891 MORTON, CHARLES A., 14, Vyvyan terrace, Clifton, Bristol.

1875 MORTON, JOHN, M.B., Guildford.

1884 MOTT, FREDERICK WALKER, M.D., F.R.S., 25, Nottingham place, W. (C. 1891-3. V.-P. 1899-1901.)

1900 MUIR, ROBERT, M.D., 4, Alfred terrace, Glasgow.

1893 MUMMERY, JOHN HOWARD, 10, Cavendish place, W.

1876 MUNRO, WILLIAM, M.D., C.M., 13, King William street, E.C.

1899 MURRAY, GEORGE R., M.D., 11, Ellison place, Newcastle-on-Tyne.

1885 MURRAY, HUBERT MONTAGUE, M.D., 25, Manchester square, W. (C. 1896-9.)

1894 MURRAY, JOHN, M.B., B.Ch., 110, Harley street, W.

1901 NABARRO, DAVID, M.D., B.Sc., D.P.H., 6, Crown Office Row, Inner Temple, E.C.

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Elected

1887 NASON, EDWARD NOEL, M.D., 80, Abbey street, Nuneaton.
1875 NEWBY, CHARLES HENRY, 63, Victoria road North, Southsea, Hants.
1902 NEWLAND, THOMAS SIMPSON, M.B., Ch.B., North terrace, Adelaide, S. Australia.
1884 NEWLAND-PEDLEY, FREDERICK, 32, Devonshire place, Portland place, W.
1865 NEWMAN, WILLIAM, M.D., Stamford, Lincolnshire.
1895 NIAS, J. BALDWIN, M.D., 5, Rosary gardens, S. Kensington, S.W.
1868 NICHOLLS, JAMES, M.D., Trekenning House, St. Columb, Cornwall.
1876 NICHOLSON, FRANK, M.D., 29, Albion street, Hull.
1864 **NORTON**, ARTHUR T., C.B., Leyfields Wood, Ashampstead, Berks. (C. 1877-9.)
1883 NORVILL, FREDERIC HARVEY, M.B., Dibrooghur, India.
1856 NUNN, THOMAS WILLIAM, 8, Stratford place, W. (C. 1864-6. V.-P. 1878-80.)

1880 O'CONNOR, BERNARD, M.D., 25, Hamilton road, Ealing.
1873 O'FARRELL, Sir GEORGE PLUNKETT, M.D., 19, Fitzwilliam square, Dublin.
1894 OGLE, CYRIL, M.B., 96, Gloucester place, W. (C. 1899-1901.)
1876 OLIVER, JOHN FERENS, M.D., 12, Old Elvet, Durham.
1888 OPENSHAW, THOMAS HORROCKS, M.S., 16, Wimpole street, W.
1892 ORD, WILLIAM WALLIS, M.D., The Hall, Salisbury.
1879 ORMEROD, JOSEPH A., M.D., 25, Upper Wimpole street, W. (C. 1887-9.)
1875 **OSBORN**, SAMUEL, 1A, Devonshire street, W., and Maisonnette, Datchet, Bucks.
1881 OWEN, Sir ISAMBARD, M.D., 40, Curzon street, W.
1865 OWLES, JAMES ALLDEN, M.D., Hill View, Woking, Surrey.

1884 PAGET, STEPHEN, 70, Harley street, W. (C. 1894-7.)
1895 PAKES, WALTER CHARLES, Government Laboratory, Pretoria, South Africa. (C. Com. Sect. B, 1901-2.)
1897 PARFITT, CHARLES D., M.D., London, Canada.
1898 PARKER, ARTHUR PERCY, M.B., B.Ch., 27, Beaumont street, Oxford.
1874 PARKER, RUSHTON, M.B., B.S., 59, Rodney street, Liverpool.
1853 **PARKINSON**, GEORGE, Halsdown House, Exmouth, South Devon.
1901 PARSONS, JOHN HERBERT, M.B., B.S., B.Sc., 28, Great Ormond street, W.C.
1882 PASTEUR, WILLIAM, M.D., 4, Chandos street, W. (C. 1893-6.)
1885 PAUL, FRANK THOMAS, 38, Rodney street, Liverpool.
1865 **PAVY**, FREDERICK WILLIAM, M.D., LL.D., F.R.S., 35, Grosvenor street, W. (C. 1872-4. V.-P. 1891-2. V.-P., Chairman Sect. C, 1901—. P. 1893-4.)
1868 PAYNE, JOSEPH FRANK, M.D. (TRUSTEE), 78, Wimpole street, W. (M.G.C. 1872-85. C. 1873-5, 1883-5. S. 1880-2. V.-P. 1888-9. V.-P., Chairman Sect. A, 1901-2. P. 1897-8.)
1872 PEARCE, JOSEPH CHANING, M.D., C.M., Montague House, St. Lawrence-on-Sea, Kent.
1879 PEEL, ROBERT, 130, Collins street East, Melbourne, Victoria.
1899 PEMBREY, MARCUS SEYMOUR, M.D., B.Ch., Guy's Hospital, S.E.

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Elected

1889 PENBERTHY, JOHN, Royal Veterinary College, Camden Town, N.W.
1887 PENROSE, FRANCIS GEORGE, M.D., 84, Wimpole street, W.
1884 PEPPER, AUGUSTUS JOSEPH, M.B., C.M., 13, Wimpole street, W.
1900 PERKINS, JOSEPH JOHN, M.B., 41, Wimpole street, Cavendish square, W.
1899 PERNET, GEORGE, 77, Upper Gloucester place, N.W.
1888 PERRY, EDWIN COOPER, M.D., Superintendent's House, Guy's Hospital, S.E.
1902 PHEAR, ARTHUR G., M.D., 47, Weymouth street, W.
1878 PHILIPPS, SUTHERLAND REES, M.D., St. Ann's heath, Virginia Water, Chertsey.
1878 PHILLIPS, JOHN WALTER, 30, Stanley street West, Melbourne, Victoria.
1896 PIGG, T. STRANGEWAYS, St. John's College, Cambridge.
1893 PINKERTON, ROBERT A., M.A., M.D., 15, South Norwood hill, S.E.
1884 PITT, GEORGE NEWTON, M.D., 15, Portland place, W. (M.G.C. 1889-97. C. 1890-2, 1896-9. S. 1894-6. V.-P. 1899-1901.)
1876 PITTS, BERNARD, M.A., M.C., 109, Harley street, W. (C. 1888-90.)
1899 PLIMMER, HENRY GEORGE, 28, St. John's Wood road, N.W. (C. Com. Sect. B, 1901—.)
1883 POLAND, JOHN, 2, Mansfield street, Cavendish square, W.
1882 POLLARD, BILTON, M.B., B.S., 24, Harley street, W. (C. 1895-7.)
1850 POLLOCK, JAMES EDWARD, M.D., 37, Collingham place, W. (C. 1862-4. V.-P. 1879-81.)
1870 POORE, GEORGE VIVIAN, M.D., 24A, Portland place, W. (C. 1883-5.)
1879 **POTTER**, HENRY PERCY, M.D., St. Mary Abbotts Infirmary, Marloes road, Kensington, W.
1866 POWELL, Sir RICHARD DOUGLAS, Bart., K.C.V.O., M.D., 62, Wimpole street, W. (C. 1873-5, 1881-3. S. 1877-9. V.-P. 1887-8.)
1884 POWER, D'ARCY, M.A., M.B., 10A, Chandos street, W. (C. 1891-3. 1899-1902. Com. Sect. A, 1901-2. M.G.C. 1897-1900. S. 1897-9.)
1865 POWER, HENRY, 37A, Great Cumberland place, W. (C. 1876-7.)
1900 POYNTON, FREDERICK JOHN, M.D., 8, Queen Anne street, Cavendish square, W.
1887 PRATT, WILLIAM SUTTON, M.D., Penrhos House, Rugby.
1902 PRICE, F. W., M.B., City of London Hospital for Diseases of the Chest, Victoria park, E.
1884 PRICE, JOHN A. P., M.D., 124, Castle street, Reading.
1900 PRICE-JONES, CECIL, M.B., 7, Claremont road, Surbiton, Surrey.
1888 PRIMROSE, ALEXANDER, M.B., C.M., 100, College street, Toronto, Canada.
1882 PRINGLE, JOHN J., M.B., C.M., 23, Lower Seymour street, W.
1895 PURVIS, WILLIAM PRIOR, M.D., 2, Avenue place, Southampton.
1865 PYE-SMITH, PHILIP HENRY, M.D., F.R.S., 48, Brook street, W. (C. 1874-7. V.-P. 1890-1.)

1897 RANKIN, GUTHRIE, M.D., 4, Chesham street, S.W.
1890 **Ransom**, WILLIAM BRAMWELL, M.D., The Pavement, Nottingham.
1891 RATCLIFFE, JOSEPH RILEY, M.B., C.M., Wake green, Moseley.
1887 RAVEN, THOMAS FRANCIS, Broadstairs, Kent.
1870 RAY, EDWARD REYNOLDS, 15A, Upper Brook street, W.
1875 REID, ROBERT WILLIAM, M.D., C.M., 8, Queen's gardens, Aberdeen,

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1901 REID, ST. GEORGE CAULFIELD, Brigstock House, Thornton Heath, Surrey.
1901 REISSMANN, CHARLES, M.B., 7, Upper Montague street, Russell square, W.C.
1881 RENNER, WILLIAM, Wilberforce street, Free Town, Sierra Leone.
1893 RENNIE, GEORGE EDWARD, M.D., College street, Hyde park, Sydney, N.S.W.
1899 RICHMOND, BENJAMIN ARTHUR, M.B., B.S., B.Sc., 154, Jamaica road, Bermondsey, S.E.
1895 RITCHIE, JAMES, M.D., 28, Beaumont street, Oxford.
1901 RIVIERE, CLIVE, M.D., 82, Finchley road, N.W.
1865 **Roberts**, DAVID LLOYD, M.D., 11, St. John's street, Manchester.
1871 ROBERTS, FREDERICK THOMAS, M.D., 102, Harley street, W. (C. 1883-5.)
1878 ROBERTS, WILLIAM HOWLAND, M.D., Surgeon, Madras Army.
1888 ROBERTSON, ROBERT, M.D., The Bungalow, Ventnor, Isle of Wight.
1885 ROBINSON, ARTHUR HENRY, M.D., St. Mary's Infirmary, Highgate Hill, N.
1882 ROBINSON, TOM, M.D., 9, Princes street, Cavendish square, W.
1897 ROGER-SMITH, HUGH, M.D., 1, College terrace, Fitzjohn's avenue, N.W.
1888 ROLLESTON, HUMPHRY DAVY, M.A., M.D. 55, Upper Brook street, Grosvenor square, W. (C. 1894-7. 1900-1902. Com. Sect. A, 1901-2. M.G.C. 1895-1900. S. 1898-1900.)
1858 **ROSE**, HENRY COOPER, M.D., 16, Warwick road, Maida hill, N.W. (C. 1873-4.)
1875 ROSSITER, GEORGE FREDERICK, M.B., Cairo Lodge, Weston-super-Mare.
1877 **ROTH**, BERNARD, 38, Harley street, W., and "Wayside," 1, Preston park avenue, Brighton.
1888 ROUGHTON, EDMUND WILKINSON, M.D., 38, Queen Anne street, W.
1891 ROUILLARD, LAURENT ANTOINE JOHN, M.B., Durban, Natal.
1901 ROWLAND, SYDNEY, M.A., Palace Chambers, Westminster, S.W.
1899 ROWLANDS, ROBERT P., Guy's Hospital, S.E.
1891 RÜFFER, MARC ARMAND, M.D., The Quarantine Board, Alexandria.
1897 RUNDLE, HENRY, 13, Clarence parade, Southsea.
1900 RUSSELL, A. E., M.D., St. Thomas's Hospital, S.E.
1895 RUSSELL, JAMES SAMUEL RISIEN, M.D., 44, Wimpole street, Cavendish square, W.
1891 RUSSELL, WILLIAM, M.D., 3, Walker street, Edinburgh.

1854 SANDERSON, Sir JOHN BURDON, Bart., M.D., D.C.L., F.R.S., 64, Banbury road, Oxford. (M.G.C. 1869-76. C. 1864-7. V.-P. 1873-4.)
1897 SANTI, PHILIP R. W. DE, 15, Stratford place, W.
1902 SARGENT, PERCY WILLIAM GEORGE, M.B., B.C., St. Thomas's Hospital, S.E.
1886 SAUNDBY, ROBERT, M.D., 140B, Great Charles street, Birmingham.
1871 SAUNDERS, CHARLES EDWARD, M.D., Sussex County Lunatic Asylum, Haywards Heath.
1901 SAUNDERS, E. A., M.B., 49, Harley street, W.
1890 SAUNDERS, FREDERICK WILLIAM, M.B., B.C., Chieveley House, Newbury.

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1873 SAVAGE, GEORGE HENRY, M.D., 3, Henrietta street, Cavendish square, W. (C. 1881-3.)

1882 SAVILL, THOMAS DIXON, M.D., 60, Upper Berkeley street, W.

1902 SCHÖLBERG, H. A., M.B., St. Bartholomew's Hospital, E.C.

1891 SCHORSTEIN, GUSTAVE ISIDORE, M.B., B.Ch., 11, Portland place, W.

1901 SCOTT, Hon. G. H., M.B., B.C., Mertoun House, St. Boswells, N.B.

1902 SCOTT, S. G., St. Thomas's Hospital, S.E.

1899 SELIGMANN, CHARLES G., M.B., 23, Vincent square, S.W.

1877 SEMON, Sir FELIX, M.D., 39, Wimpole street, W. (C. 1885-7.)

1894 SEQUEIRA, JAMES HARRY, M.D., 13, Welbeck street, Cavendish square, W.

1872 SERGEANT, EDWARD, D.P.H., Lancashire County Council, Public Health Department, County Offices, Preston.

1876 SHARKEY, SEYMOUR J., M.D., 22, Harley street, W. (M.G.C. 1884-1895. C. 1884-6. V.-P. 1895-7.)

1880 SHATTOCK, SAMUEL G. (HON. GENERAL SECRETARY), 4, Crescent road, The Downs, Wimbledon, S.W. (M.G.C. 1884-1900. C. 1885-7, 1893-6. S. 1890-2, 1902—. V.-P. 1896-8. E. 1900—.)

1898 SHAW, HAROLD BATTY, M.D., 7, Devonshire street, W.

1885 SHAW, LAURISTON ELGIE, M.D., 64, Harley street, W.

1886 **SHERRINGTON**, CHARLES SCOTT, M.D., F.R.S., University College, Liverpool. (C. 1894-7.)

1856 **SHILLITOE**, BUXTON, 2, Frederick's place, E.C.

1875 SIDDALL, JOSEPH BOWER, M.D., C.M., Conybeare, Northam, Bideford.

1880 SILCOCK, A. QUARRY, M.D., B.S., 52, Harley street, W. (C. 1888-90.)

1901 SINGER, HAROLD DOUGLAS, M.D., St. Thomas's Hospital, S.E.

1866 SIMS, FRANCIS MANLEY BOLDERO, 12, Hertford street, W.

1892 SLATER, CHARLES, M.B., St. George's Hospital, S.W.

1887 SMALLPEICE, WILLIAM DONALD, 42, Queen Anne's gate, S.W.

1879 SMITH, E. NOBLE, 24, Queen Anne street, W.

1887 SMITH, FREDERICK JOHN, M.D., 138, Harley street, W.

1875 SMITH, GEORGE JOHN MALCOLM, M.D., Hurstpierpoint, Sussex.

1894 SMITH, GUY BELLINGHAM, M.B., B.S., 24, St. Thomas's street, S.E.

1900 SMITH, J. LORRAIN, M.D., Queen's College, Belfast.

1873 SMITH, RICHARD T., M.D., 117, Haverstock hill, N.W.

1883 SMITH, ROBERT PERCY, M.D., 36, Queen Anne street, W.

1869 SMITH, ROBERT SHINGLETON, M.D., Deepholm, Clifton Park, Bristol.

1892 SMITH, SOLOMON CHARLES, M.D., Four Oaks, Walton-on-Thames, Surrey.

1856 SMITH, Sir THOMAS, Bart., 5, Stratford place, W. (C. 1867-9. V.-P. 1877-8.)

1866 SMITH, WILLIAM, Melbourne, Australia.

1870 SMITH, WILLIAM JOHNSON, Seamen's Hospital, Greenwich, S.E. (C. 1879-81.)

1870 SNOW, WILLIAM VICARY, M.D., Richmond Gardens, Bournemouth.

1888 SOLLY, ERNEST, M.B., Strathlea, Harrogate, Yorks.

1887 SPENCER, WALTER GEORGE, M.S., 35, Brook street, W. (M.G.C. 1894-1900. C. 1896-9.)

1899 SPRIGGS, EDMUND IVENS, M.D., 24, St. Thomas's street, S.E.

1861 SQUIRE, ALEXANDER BALMANNO, M.B., 24, Weymouth street, W.

1890 STABB, EWEN CARTHEW, 57, Queen Anne street, W.

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1901 STAINER, E., M.B., 60, Wimpole street, W.

1895 STARLING, ERNEST HENRY, M.D., F.R.S., 8, Park square West, Regent's Park, N.W. (C. Com. Sect. C, 1901—.)

1896 STEPHENS, J. W. W., M.D., 8, Fopstone road, Earl's Court.

1899 STEWARD, FRANCIS J., M.S., 24, St. Thomas's street, S.E.

1900 STEWART, PURVES, M.D., 7, Harley street, W.

1891 STILES, HAROLD JALLAND, M.B., C.M., 5, Castle terrace, Edinburgh.

1897 STILL, GEORGE F., M.D., 114, Harley street, W. (C. Com. Sect. A, 1901—.)

1879 STIRLING, EDWARD CHARLES, C.M.G., M.D., F.R.S., Adelaide, South Australia [care of Messrs. Elder & Co., 7, St. Helen's place, E.C.].

1883 STOKER, GEORGE, 14, Hertford street, W.

1884 STONHAM, CHARLES, 4, Harley street, W. (C. 1893-6.)

1875 STURGE, W. A., M.D., 29, Boulevard Dubouchage, Nice.

1867 SWAIN, WILLIAM PAUL, 17, The Crescent, Plymouth.

1881 SYMONDS, CHARTERS JAMES, M.S., 58, Portland place, W. (M.G.C. 1884-91. C. 1886-8. V.-P. 1899-1901.)

1886 TARGETT, JAMES HENRY, M.B., M.S., 6, St. Thomas's street, S.E. (M.G.C. 1894-1900. C. 1894-5, 1897-1900. V.-P. 1900-1902. S. 1895-7.)

1870 TAY, WARREN, 4, Finsbury square, E.C. (C. 1881-2.)

1871 **TAYLOR**, FREDERICK, M.D., 20, Wimpole street, W. (M.G.C. 1879-89. C. 1879-81. V.-P. 1897-9.)

1885 TAYLOR, HENRY H., 10, Brunswick place, Hove, Sussex.

1892 TAYLOR, JAMES, M.D., 49, Welbeck street, W.

1902 THIELE, FRANCIS HUGO, M.D., 7, Hampstead lane, Highgate, N.

1879 THIN, GEORGE, M.D., 63, Harley street, W. (C. 1889-90.)

1852 **THOMPSON**, Sir HENRY, Bart., 35, Wimpole street, W. (S. 1859-63. C. 1865-7. V.-P. 1868-70.)

1897 THOMSON, H. CAMPBELL, M.D., 34, Queen Anne street, W.

1891 THOMSON, HENRY ALEXIS, M.D., 32, Rutland square, Edinburgh.

1884 THOMSON, JOHN, M.D., C.M., 14, Coates crescent, Edinburgh.

1901 THOMSON-WALKER, J. W., M.B., 8, Cavendish place, W.

1892 **Thorburn**, WILLIAM, B.S., 2, St. Peter's square, and Rusholme Lodge, Rusholme, Manchester.

1874 THORNTON, JOHN KNOWSLEY, M.B., Hildersham Hall, Cambridge.

1872 THORNTON, WILLIAM PUGIN, 35, St. George's place, Canterbury.

1900 THURSFIELD, HUGH, M.D., 10, Bentinck street, W.

1880 TIRARD, NESTOR ISIDORE, M.D., 74, Harley street, W.

1884 TIVY, WILLIAM JAMES, 8, Lansdowne place, Clifton, Bristol.

1901 TODD, CHARLES, M.D., Queensberry Lodge, Aldenham, Herts.

1897 TOOGOOD, F. SHERMAN, M.D., The Infirmary, 282, High street, Lewisham, S.E.

1882 TOOTH, HOWARD HENRY, C.M.G., M.D., 34, Harley street, W. (C. 1892-4. M.G.C. 1895-1900.)

1886 TOTSUKA, KANKAI, Tokio, Japan.

1872 **TOWNSEND**, THOMAS SUTTON, 68, Queen's gate, S.W.

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1899 TREDGOLD, ALFRED F., London County Asylum, Woodford Bridge, Essex.
1888 TREVELYAN, EDMOND F., M.D., 40, Park square, Leeds.
1881 TREVES, Sir FREDERICK, Bart., C.B., K.C.V.O., 6, Wimpole street, W. (C. 1887-90. V.-P. 1895-7.)
1851 TROTTER, JOHN W., 4, St. Peter's terrace, York. (C. 1865-9.)
1895 TROUTBECK, HENRY, M.B., B.C., 148, Ashley gardens, S.W.
1859 **TRUMAN**, EDWIN THOMAS, 23, Old Burlington street, W.
1888 TUBBY, ALFRED HERBERT, M.S., 25, Weymouth street, Portland place, W.
1867 TUCKWELL, HENRY MATTHEWS, M.D., 64, High street, Oxford.
1858 TUDOR, JOHN, Dorchester, Dorset.
1863 TURNER, JAMES SMITH, 12, George street, Hanover square, W.
1893 TURNEY, HORACE GEORGE, M.D., M.Ch., 68, Portland place, W.
1858 **TURTLE**, FREDERICK, M.D., Kirkmead, Woodford, Essex.
1880 TYSON, WILLIAM JOSEPH, M.D., 10, Langhorne gardens, Folkestone.

1867 VENNING, EDGCOMBE, 30, Cadogan place, S.W.
1889 VOELCKER, ARTHUR FRANCIS, M.D., B.S., 31, Harley street, W. (C. 1895-7.)

1867 **WAGSTAFFE**, WILLIAM WARWICK, B.A., Purleigh, St. John's hill, Sevenoaks. (C. 1874, 1878-80. M.G.C. 1874-82. S. 1875-7.)
1885 WAKLEY, THOMAS, jun., 5, Queen's gate, S.W.
1902 WALKER, E. W. AINLIE, M.D., 40, Devonshire street, Portland place, W.
1893 WALKER, NORMAN PURVIS, M.D., 7, Manor place, Edinburgh.
1901 WALLACE, CUTHBERT SIDNEY, 26, Upper Wimpole street, W.
1881 WALLER, BRYAN CHARLES, M.D., Masongill House, Cowan bridge, Kirkby-Lonsdale.
1890 WALLIS, FREDERICK CHARLES, M.B., B.C., 107, Harley street, W. (C. 1898-1901.)
1888 WALSHAM, HUGH, M.A., M.D., B.C., 114, Harley street, W.
1873 **WALSHAM**, WILLIAM JOHNSON, M.B., C.M., 77, Harley street, W. (C. 1881-3.)
1859 WALTERS, JOHN, M.B., Reigate, Surrey.
1892 WARD, ALLAN OGIER, M.D.Edin., 73, Cheapside, E.C.
1892 WARING, HOLBURT JACOB, M.B., M.S., 37, Wimpole street, W.
1901 WARNER, ALLAN, M.D., 5, Ferndale villas, Harrow.
1891 WATERHOUSE, HERBERT FURNIVALL, M.D., C.M., 81, Wimpole street, W.
1892 WEAVER, FREDERICK POYNTON, M.D., Cedar Lawn, Hampstead Heath, N.W.
1890 WEBB, CHARLES FREER, M.D., New street House, Basingstoke.
1894 **WEBER**, FREDERICK PARKES, M.D., 19, Harley street, W.
1858 **WEBER**, Sir HERMANN, M.D., 10, Grosvenor street, W. (C. 1867-70. V.-P. 1878-80.)
1864 WELCH, THOMAS DAVIES, M.D. (Travelling).
1894 WELLS, SYDNEY RUSSELL, M.D., 24, Somerset street, Portman square, W.

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1892 WESBROOK, FRANK F., M.D., The University of Minnesota, Minneapolis, U.S.A.

1877 WEST, SAMUEL, M.D., 15, Wimpole street, W. (C.1884-6, 1891-3. S. 1889-90. V.-P. 1896-7.)

1888 WETHERED, FRANK J., M.D., 83, Harley street, W.

1891 WHEATON, SAMUEL WALTON, M.D., 10, Restall avenue, Streatham hill, S.W.

1867 WHIPHAM, THOMAS TILLYER, M.D., 11, Grosvenor street, W. (C. 1880-2.)

1869 WHIPPLE, JOHN H. C., M.D., Royal Army Medical Corps.

1877 WHITE, CHARLES HAYDON, 20, Shakespeare street, Nottingham.

1894 WHITE, CHARLES POWELL, M.B., 2, Blandford Gardens, Woodhouse Lane, Leeds.

1891 WHITE, GILBERT B. MOWER, M.B., B.S., 112, Harley street, W.

1881 WHITE, WILLIAM HALE, M.D., 65, Harley street, W. (C. 1888-90.)

1886 WHITE, WILLIAM HENRY, M.D., 43, Weymouth street, W.

1868 **Whitehead**, WALTER, 17, Market street, Manchester.

1897 WHITFIELD, ARTHUR, M.D., 12, Upper Berkeley street, Portman square, W.

1870 WICKSTEED, FRANCIS WILLIAM, 2, Prince's mansions, Victoria street, S.W.

1869 WILKIN, JOHN F., M.D., M.C., Rose Ash House, South Molton, N. Devon.

1871 WILKINSON, J. SEBASTIAN, The Laurels, Oakengates, Salop.

1879 WILLCOCKS, FREDERICK, M.D., 14, Mandeville place, W.

1869 WILLIAMS, ALBERT, M.D. (Travelling).

1858 **Williams**, CHARLES, 48, Prince of Wales road, Norwich.

1866 WILLIAMS, CHARLES THEODORE, M.D., 2, Upper Brook street, W. (C. 1875-8.)

1881 WILLIAMS, DAWSON, M.D., B.S., 2, Wyndham place, Bryanston square, W. (C.1893-6.)

1872 WILLIAMS, Sir JOHN, Bart., M.D., 63, Brook street, W. (C. 1878-80.)

1881 WILLIAMS, W. ROGER, Beaufort House, Clifton Down, Clifton.

1900 WILLIAMSON, OLIVER K., M.B., B.C., 55, Upper Berkeley street, W.

1863 WILLIS, FRANCIS, M.D., Asheville, N. Carolina, U.S.A.

1889 WILSON, ALBERT, M.D., Leytonstone, Essex.

1888 WILSON, CLAUDE, M.D., C.M., Church road, Tunbridge Wells.

1859 WILSON, EDWARD THOMAS, M.B., Montpelier terrace, Cheltenham.

1891 WILSON, THEODORE STACEY, M.D., C.M., 29, Temple row, Birmingham.

1861 **Windsor**, THOMAS, Medical Library, Boston, Mass., U.S. [care of B. F. Stevens, 4, Trafalgar square, W.].

1889 WINGRAVE, V. HAROLD WYATT, 11, Devonshire street, Portland place, W.

1874 WISEMAN, JOHN GREAVES, Dearden street, Ossett, Yorkshire.

1865 WITHERBY, WILLIAM H., M.D., Pitt place, Coombe, Croydon.

1883 WOODCOCK, JOHN ROSTRON, Abberley, near Stourport, Worcestershire.

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Elected

1883 WOODHEAD, GERMAN SIMS, M.D., 6, Scrope terrace, Cambridge. (C. 1891-3. V.-P. 1898—1900. M.G.C. 1899—1900.)

1879 WOODWARD, G. P. M., M.D., Deputy Surgeon General; Sydney, New South Wales.

1884 WORTS, EDWIN, 6, Trinity street, Colchester.

1890 WYNNE, EDWARD T., M.B., Gladstone, Queensland.

1884 WYNTER, WALTER ESSEX, M.D., 30, Upper Berkeley street, W.

1872 YOUNG, HENRY, M.B., Monte Video, South America.

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ANNUAL REPORT OF COUNCIL,

1901-2.

PRESENTED AT THE ANNUAL MEETING, MAY 20TH, 1902.

YOUR Council have to report that during the last session thirty-nine new members have been elected into the Society.

Thirteen members have resigned, and there have been ten losses by death.

The total number of members is now 713, of whom thirteen are honorary members.

The death-roll this year includes Mr. Thomas Bond, Mr. John Griffith, Mr. Carsten Holthouse, Mr. A. H. Smee, Dr. James Mann Williamson, Sir W. MacCormac, Dr. W. M. Ord, Dr. Henry Sutherland, Mr. William Tickle Whitmore, and Mr. Athol A. W. Johnstone.

Mr. Holthouse was an Original Member of the Society, and was the last of the Original Members.

Sir William MacCormac served on the Council from 1878 to 1880.

Dr. William Miller Ord was a Vice-President in 1893-4, and took, as is well known, a very active part in the work of the Society. He communicated many papers of interest and value to its 'Transactions.'

The rearrangement of the Society's meetings has led to a gratifying increase in the attendance of members. Four laboratory meetings have also been held in the laboratories of the Jenner Institute of Preventive Medicine, of King's College, of the Royal Colleges of Physicians and Surgeons, and in the Medical School of the Middlesex Hospital.

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The President and General Secretary attended the celebration of Prof. Virchow's eightieth birthday in Berlin on October 12th, 1901, and presented to him a congratulatory address on behalf of the Society.

The Society's financial year, which opened with a balance of £37 13*s.* 5*d.*, closes with an overdraft on its bankers to the extent of £76 1*s.* 10*d.*, a sum which includes £3 1*s.* 2*d.* withdrawn for petty cash disbursements, and as yet unexpended. This year, as in the preceding, the expenditure has been considerably in excess of income, and for the same reason, namely, the larger amount spent in the production of the 'Transactions.' The income from all sources was £488 18*s.* 4*d.*, the total expenditure £599 12*s.* 5*d.* There are still some subscriptions outstanding, but the liabilities include the cost of the General Index, which has now left the printers' hands. It will, therefore, be necessary shortly to effect the sale of stock sanctioned last year, but deferred owing to the state of the funds due to the war. It will also be necessary to consider in what direction retrenchment can be carried out, so as to bring the annual expenditure within the limits of the Society's income.

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THE PATHOLOGICAL SOCIETY OF LONDON.

Statement of Receipts and Payments from 15th May, 1901, to 15th May, 1902.

RECEIPTS.

	£	s.	d.	£	s.	d.
Balance at Bank—May, 1901	36	4	2			
,, in hand—Petty Cash, etc.	1	9	3			
				37	13	5
329 Subscriptions at £1 1s.	345	9	0			
32 Entrance Fees at £1 1s.	33	12	0			
3 ,, Non-Resident (Old Regulations)	9	9	0			
1 Life Composition Fee	10	10	0			
				399	0	0
Sale of Transactions:						
Publisher				61	1	4
Dividends on Consols				28	17	0
				526	11	9
Balance due to Bank				76	1	10
				£602	13	7

PAYMENTS.

	£	s.	d.	£	s.	d.
Meetings:						
Rent of Rooms	73	10	0			
Refreshments and Attendance at Meetings	23	0	0			
Microscopes	21	6	6			
Reporting Meetings	3	0	0			
				120	16	6
Transactions:						
Printing, Binding, etc., for Vol. LII	218	8	4			
Illustrations ,, ,,	106	2	0			
Editor ,, ,,	50	0	0			
Illustrations for Vol. LIII	1	10	0			
				376	0	4
Secretariat and Treasury:						
General Printing and Stationery	41	7	1			
Council Notices	2	12	9			
Typing Reports	2	6	11			
Secretarial Assistance	15	15	0			
Collection of Subscriptions	15	15	0			
Mr. Clarke's Fee	5	5	0			
				83	1	9
Inscribing Address to H.M. the King / Illuminated Address to Prof. Virchow				9	13	0
Returned Subscriptions paid in error				2	2	0
Petty Cash Expenditure				7	13	1
Bank Charges				0	5	9
				599	12	5
Petty Cash in hand				3	1	2
				£602	13	7

Audited and approved, 16th May, 1902.

SIDNEY COUPLAND, *Treasurer.*
JOHN ROSE BRADFORD, *Hon. Secretary.*

RAYMOND JOHNSON,
ARTHUR G. PHEAR, } *Auditors.*

NOTE.—The sum of £1114 3*s.* 2*d.* is invested in Consols.

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REPORT.

SESSION 1901–1902.

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1. *Degenerations following a traumatic lesion of the spinal cord, with an account of a tract in the cervical region.*

By Purves Stewart.

[With Plates I, II, III.]

The case upon which the following paper is based was that of a female patient, aged 28, in the Westminster Hospital, who sustained a dislocation of the vertebral column between the bodies of the fifth and sixth cervical vertebræ, crushing the spinal cord at the upper part of the seventh segment for a vertical extent of about half an inch. The patient survived for ten weeks after the injury. (For the clinical record see 'Brain,' 1900, vol. xxiii, pp. 139—156.)

The whole spinal cord, the medulla oblongata, and the pons Varolii were obtained for examination. Sections of the pons, medulla, and cord were stained by the Marchi method, together with the anterior and posterior nerve-roots of both sides, from the fifth cervical to the first thoracic inclusive. The segments of

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the cord in the vicinity of the lesion, both above and below, were stained by the Thionin-Nissl and by van Gieson's hæmatoxylin and picro-fuchsin methods; segments from the mid-thoracic and mid-lumbar regions were also examined by the latter methods.

Extent of Lesion.

At the upper part of the seventh cervical segment the cord was abruptly flattened to a thin ribbon, measuring only 1 mm. in antero-posterior thickness (*see* Pl. II). Below that level there were hæmorrhages within the cord, extending, on the right side, through the grey matter and in the ventral part of the posterior column as low down as the lower part of the eighth cervical segment, and on the left side to a similar situation as far as the lower part of the seventh cervical segment; no hæmorrhage extended upwards on the cephalic side of the lesion beyond the immediate vicinity of the injury. None of the nerve-roots, anterior or posterior, were torn across. On examination of the *anterior nerve-roots* on both sides, from the third cervical to the first thoracic inclusive, the *seventh cervical pair* were alone found degenerated. All the corresponding posterior nerve-roots of both sides were quite free from degeneration in their extra-medullary course, as shown by the Marchi stain.

Explanation of Illustrations.

In the case of the spinal cord it should be noted that the most caudal part of every segment, from the uppermost cervical to the coccygeal, was systematically chosen for examination. In the medulla and pons thin slices were examined at short distances from each other. In every instance the section was magnified ten times and traced by means of Edinger's projection apparatus and the degenerations accurately filled in, partly under the projection apparatus and partly by comparison with the aid of the microscope. In this way a complete series of figures was obtained, illustrating the degenerations which had supervened in the various tracts. The figures were again photographed down to their present size.

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We shall consider the degenerations in the following order:

DESCENDING DEGENERATIONS.

(*a*) Lateral columns.
(*b*) Anterior columns.
(*c*) Posterior columns.

ASCENDING DEGENERATIONS.

(*d*) Posterior columns.
(*e*) Antero-lateral columns.

(*a*) *Descending degenerations of lateral columns.*

1. *Lateral pyramidal tract.*—This can be traced from the level of the lesion down to the lowest part of the coccygeal segment. At the level of the upper sacral region the number of its fibres rapidly diminishes, but there can be no doubt that it extends to the caudal extremity of the cord. Ludwig Müller (20) has recently maintained that no degeneration is ever found in the lateral columns below the third sacral segment, and v. Bechterew (4) and Ziehen (34) state that the tract terminates about the third or fourth sacral segment. Barker (1), in his text-book, states that a certain number of fibres can be traced into the lowest portion of the sacral region, whilst Risien Russell (27) and Déjérine and Thomas (9) state that the tract extends to the most caudal extremity of the cord. Our sections are in entire agreement with the statements of the two latter observers.

As low down as the sixth thoracic segment we observe that the outermost fibres of the crossed pyramidal tract do not reach quite to the periphery of the cord. From the seventh thoracic segment, however, down to the coccygeal region, they are adjacent to the lateral surface of the cord. The innermost fibres of the tract throughout the greater extent of the cord lie close against the grey matter, but from the fifth lumbar segment downwards the tract gradually recedes outwards and lies at some distance from the grey matter (*see* Pl. II and III).

2. *"Tract X": ventro-external to the crossed pyramidal tract.*—In the seventh and eighth cervical segments, close to the periphery of the cord, a small, sharply defined, degenerated area

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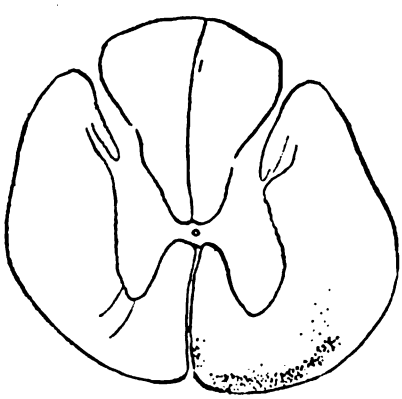
can be clearly seen at a plane corresponding to the tip of the lateral horn, ventro-external to the crossed pyramidal tract and separated from the latter by a distinct space (*see* Pl. II). It has a short course and cannot be traced below the eighth cervical segment. It is closely applied to the surface of the cord at that portion corresponding to the tip of the lateral horn of the grey matter.

Various descending tracts, in addition to those of the pyramidal system, have been described in the antero-lateral columns of the cord. Thus the vestibulo-spinal or efferent antero-lateral tract, descending from Deiters's nucleus, figured by

FIG. 1.



Descending tract from Deiters's nucleus. (Probst, *op. cit.*, Tafel vii, fig. 7.)

Ferrier and Turner (11), Risien Russell (26), Probst (24), and others, occupies the peripheral portion of the ventral part of the cord (*see* Fig. 1). But our tract is much smaller and more compact than the above, and lies farther back, in the lateral column, not in the anterior column as in the case of the vestibulo-spinal tract. Moreover "tract X" stops short at the lower end of the cervical enlargement, whereas the vestibulo-spinal tract extends caudally as far as the lumbar region.

The position of "tract X," sharply marked off by a distinct gap from the crossed pyramidal tract, also differs from that of the rubro-spinal tract described by Monakow (18) in the dog, and by Boyce (6), Held (12), and others in man, which is diffusely scattered

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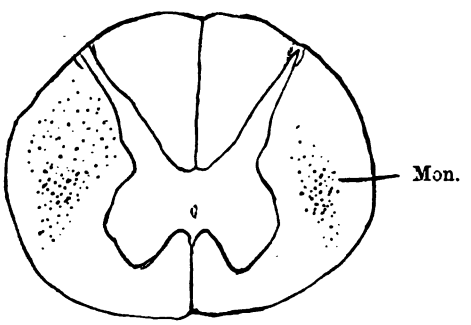
through the antero-lateral column and overlaps the area of the crossed pyramidal tract (*see* Fig. 2).

The "triangular pre-pyramidal tract," described by André Thomas (31) in the cat in a case of hemisection of the cord (*see*

FIG. 2.

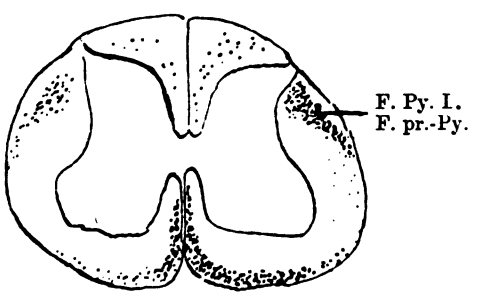


Monakow's bundle in the monkey, after a mesial lesion in Forel's decussation. (From a drawing by Dr. James Collier.)

Fig. 3), which is apposed by its base to the crossed pyramidal tract, whilst its apex is directed forwards, is probably identical, as Thomas admits, with Monakow's bundle, and like it can be traced to the lumbar region of the cord.

The descending tract from Bechterew's nucleus reticularis in

FIG. 3.



"Faisceau triangulaire pré-pyramidal," described by André Thomas (*op. cit.*, p. 49, fig. 3). Level of seventh cervical segment (cat).

the pons which, in the cord, is situated close to the anterior median fissure—"Fissurenstrang" of Tschermak—only requires to be mentioned to show that it is in no way related to the tract now under consideration.

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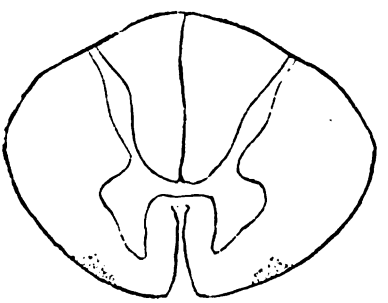
A tract corresponding somewhat more closely in position to the "tract X" is that described by Helweg (13) as the "triangular tract," and independently by von Bechterew (3) as the "olivary tract." Helweg's tract, however, lies more anteriorly than "tract X" (*see* Fig. 4). It has been a disputed point whether Helweg's tract is centrifugal or centripetal; Obersteiner (22) admits that the evidence is inconclusive one way or the other; Reinhold (25) claims to have traced Helweg's tract, although only by the Weigert-Pal method, in a case of melancholia, to the mid-thoracic region; but Bruce (7), in his recent atlas, does not find it below the third cervical segment, and Meyer (17) also traces it only to the third cervical segment, after hardening by Müller's fluid, in a case of pontine hæmorrhage. Both Reinhold and

FIG. 4.



Helweg's tract at the level of the third cervical segment. (From Bruce's 'Atlas of the Spinal Cord.')

Meyer incline to the view that it is a descending tract, which is suggested by Reinhold to be vaso-motor in function. On the other hand, von Bechterew (3), after originally stating that Helweg's tract arises "undoubtedly" from the cells of the lateral horn, proceeds in a more recent paper (5) to explain that this is merely a "topographical" expression, and that the tract is really a descending one. Edinger (10) regards Helweg's tract as an ascending one. "Tract X," however, is a descending one, and it stops short at the lower end of the cervical enlargement. Further, its position, at a plane corresponding to the tip of the lateral horn, differs from that of Helweg's tract, which lies among the anterior nerve-roots. Moreover, its degenerated fibres do not differ in average calibre from those of the crossed

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pyramidal tract, whereas both Helweg and von Bechterew agree that the "Olivenstrang" or "Dreikantenbahn" is made up of very fine fibres. Probably, however, the recent degeneration in our case renders the measurement of its individual fibres of less importance, since nerve-fibres may become considerably swollen during the process of degeneration.

On the whole, then, we may conclude that "tract X" is a descending tract which does not correspond in position to the "Dreikantenbahn" or "Olivenbündel" of Helweg and von Bechterew, and that, unlike the latter, it terminates at the lower end of the cervical enlargement.

The possibility of "tract X" being an aberrant strand of the pyramidal system must also be borne in mind. In a case such as ours, however, such an hypothesis is incapable of proof or disproof.

(*b*) *Descending degenerations of anterior columns.*

1. *Ventral pyramidal tract.*—This can be traced as a distinct band of degeneration, bounding the anterior median fissure in its whole depth, as far caudally as the third lumbar segment. Below that level the ventral fibres of the tract become scanty, and the part which extends farthest in a caudal direction is that portion which lies close to the bottom of the fissure. This latter portion of the tract can be traced as low as the lower part of the fourth sacral segment, below which level, although there are a few scattered degenerated fibres in the anterior columns, they can scarcely be dignified any longer by the name of a distinct "tract" (*see* Pl. III).

This tract is said by Barker (1) and by Ziehen (35) to end usually in the mid-thoracic region, though both of these authors admit with Tooth (32) that in rare cases it may be followed to the middle of the lumbar enlargement. Déjérine and Thomas (9), however, trace it to the fourth sacral, and Risien Russell (27) to the fifth sacral segment. Our case is again in agreement with the three latter observers.

2. *Efferent ventro-lateral tract.*—The fibres of this tract are known to be derived from various sources. Upon the discussion of these sources, the present case, being due to a bilateral spinal lesion, throws no light. The tract is seen to occupy the

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extreme periphery of the ventral portion of the cord from the anterior median fissure outwards. As low down as the fourth lumbar segment it is seen to be in close apposition with the ventral pyramidal tract. Below that level, as the ventral pyramidal tract shrinks towards the deepest part of the anterior median fissure, the efferent ventro-lateral tract remains close to the surface of the cord, and can be traced as a distinct path as far as the lower part of the fourth sacral segment. Below the fourth sacral, scattered degenerated fibres are diffusely dotted over the whole ventral part of the cord.

As we trace this tract downwards it extends less and less outwards towards the lateral aspect of the cord; the part which extends farthest caudally being that which lies near to the anterior median fissure (*see* Pl. III).

3. *Fibres in anterior commissure.*—Degenerated fibres can be traced in the "commissura alba" for three segments below the lesion, as far down as the lower part of the first thoracic segment. Below that level the anterior commissure is free from degeneration.

(*c*) *Descending degenerations of posterior columns.*

1. "*Comma*" *tract* of Schultze; *septo-marginal tract* of Bruce and Muir; *centrum ovale* of Flechsig, and *triangle médian* of Gombault and Philippe (*see* Pl. II and III).

The "comma" tract of Schultze forms a well-marked stripe of degeneration in the postero-external column of each side, extending from the dorsal aspect of the grey commissure in front to the posterior surface of the cord behind. This appearance of the tract is maintained, though its fibres gradually diminish in number from above downwards, as far caudally as the ninth thoracic segment. Below this level the ventral part of the tract disappears, whilst its superficial, most dorsal portion continues to run on caudally as the "septo-marginal" tract, whose fibres, at the level of the tenth thoracic segment, begin to bend inwards, along the dorsal surface of the cord, towards the median septum. At the eleventh thoracic segment they form a thin layer bounding the dorsal surface of the postero-internal column. In this position they run caudally for three segments (Th. 11 and 12 and L. 1). At the second lumbar

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segment they turn the corner and dip ventrally inwards into the posterior median septum. At the third, fourth, and fifth lumbar segments the fibres lie close to the median septum, and at a little distance from the dorsal surface, the tracts of the two sides here forming the "oval field" of Flechsig. At the first sacral segment the dorsal margin of the tract again reaches the surface, and from this level it can be traced in a caudal direction down to the lowest part of the coccygeal region. From the third sacral segment downwards the tracts of the two sides form a triangular area (*triangle médian* of Gombault and Philippe) whose base is situated at the dorsal surface, and whose apex extends for a short distance into the posterior median septum.

Hoche, in his classic paper (15), states that the "comma" tract is entirely separate and distinct from the combined bundle composed of the septo-marginal tract, the centrum ovale, and the triangle médian; in which view he is supported by Barker (2), who designates them as "two distinct and now fairly sharply defined descending tracts," and by Déjérine and Theohari (8), who also regard Schultze's "comma" tract as an entity anatomically independent of Hoche's peripherally situated bundle. Our case, however, tends to show that no line of demarcation can be drawn between these various bundles of descending fibres, and that they may reasonably be considered as forming, not two, but one long continuous system. Nageotti and Ettlinger (21), from a study of two cases of transverse lesion in the dorso-lumbar region, also come to this conclusion, which is also supported by Janischewsky's (16) case of lesion in the seventh cervical segment. The question as to which fibres of this system are endogenous and which exogenous in origin is not elucidated by our case, inasmuch as the lesion was one which destroyed both endogenous and exogenous fibres at the level of injury.

2. *Short descending fibres near median septum.*—In addition to the combined system of tracts already described, our sections show, as in Hoche's case, another group of descending fibres in the dorsal funiculi of the cord, lying along the posterior median septum about its middle, but not extending farther down than the eighth cervical segment. These fibres are evidently short ones, distinct from those of the "comma" tract.

Finally, a number of degenerated fibres lie scattered diffusely

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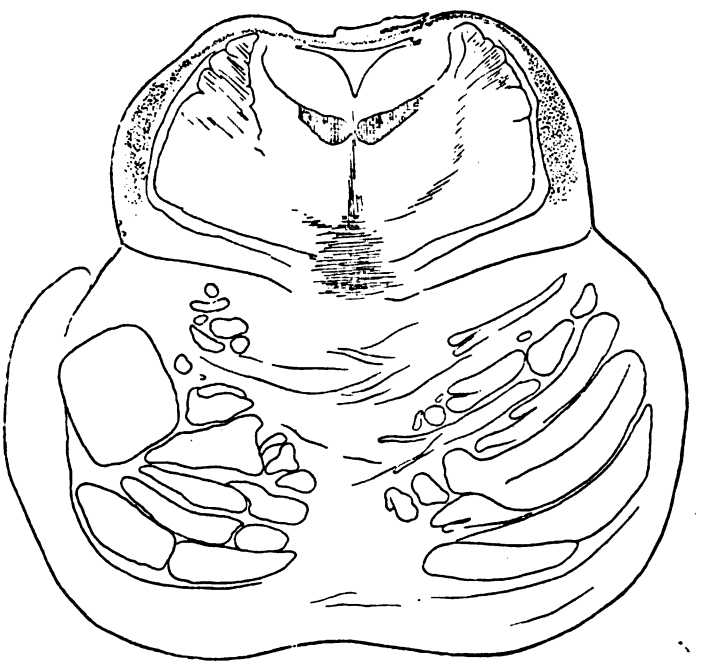
over the whole field of the posterior columns, and most abundantly near the dorsal surface of the postero-internal columns. They also stop short below the eighth cervical segment, and may probably be fairly included within the limits of "traumatic" degeneration.

(*d*) *Ascending degeneration of posterior columns.*

At the fifth cervical segment the posterior columns show well-marked degeneration over their entire area, except in a limited portion of the postero-external column in the vicinity

FIG. 5.



Level of valve of Vieussens; ascending degeneration.

of the posterior horn, where a number of undegenerated fibres are situated, having entered the cord through the posterior nerve-roots of the sixth cervical segment, above the level of the lesion. With this exception, the degeneration occupies

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the whole area of the posterior columns from the dorsal surface to the grey commissure, forming a wedge-shaped area whose apex points ventrally and is embedded in the concavity of a crescentic area of degeneration situated close to the grey matter —the "cornu-commissural zone" of Marie. Above the second cervical segment this cornu-commissural crescent disappears, and at the lower end of the first cervical segment the wedge

FIG. 6.

Upper part of pons; ascending degeneration.

alone survives, its apex touching the grey commissure. The base of the wedge at this level lies both in the postero-external and postero-internal columns; its apex lies in the postero-internal columns only (*see* Pl. I).

Sections through the lower and upper parts of the pyramidal decussation and through the lower end of the inferior olive show the blunting of the apex of the wedge by the gradual pushing backwards of the grey matter towards the dorsal surface, and the appearance, first of the nuclei graciles, and then,

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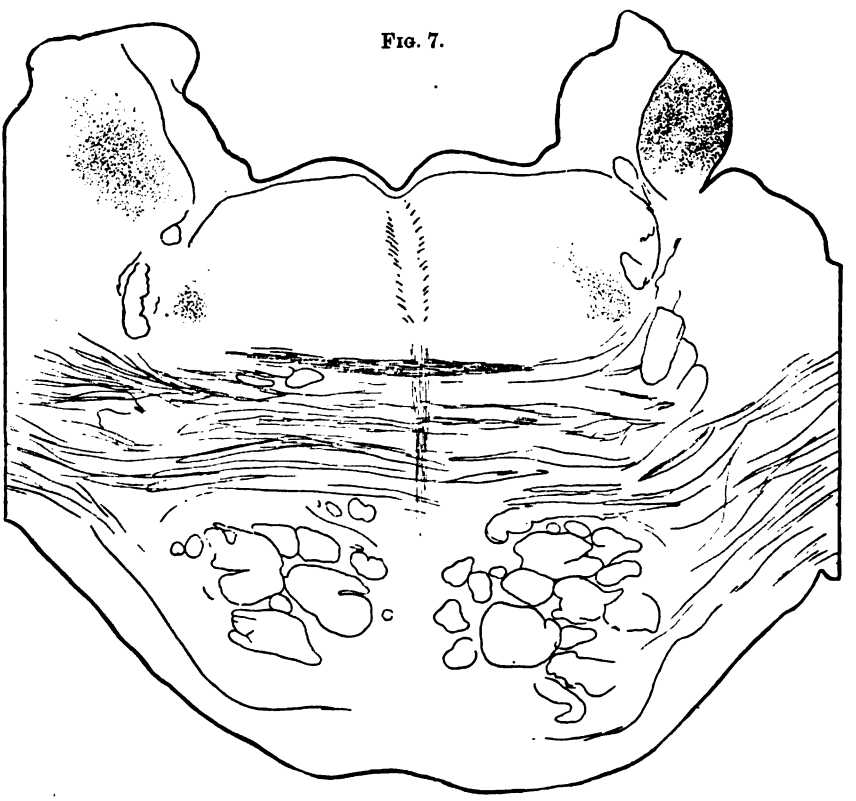
at a higher level, of the nuclei cuneati, into which nuclei, but especially the cuneate, most of the degenerated fibres are traced.

But the degeneration does not cease abruptly at the posterior column nuclei. Distinct degeneration can be seen higher up, in the arcuate fibres of the medulla, both in the postero-external arcuate fibres, on the surface of the medulla, and in the decus-

FIG. 7.



Middle of pons; ascending degeneration.

sating internal arcuate fibres. By the time the level of the lower end of the fourth ventricle is reached this degeneration of the arcuate fibres is less conspicuous, and is seen chiefly in the vicinity of the raphe. In this respect our sections entirely corroborate the results of Hoche (15), Schaffer (28), and others, although both Mott (19) and Sherrington (29) in experimental

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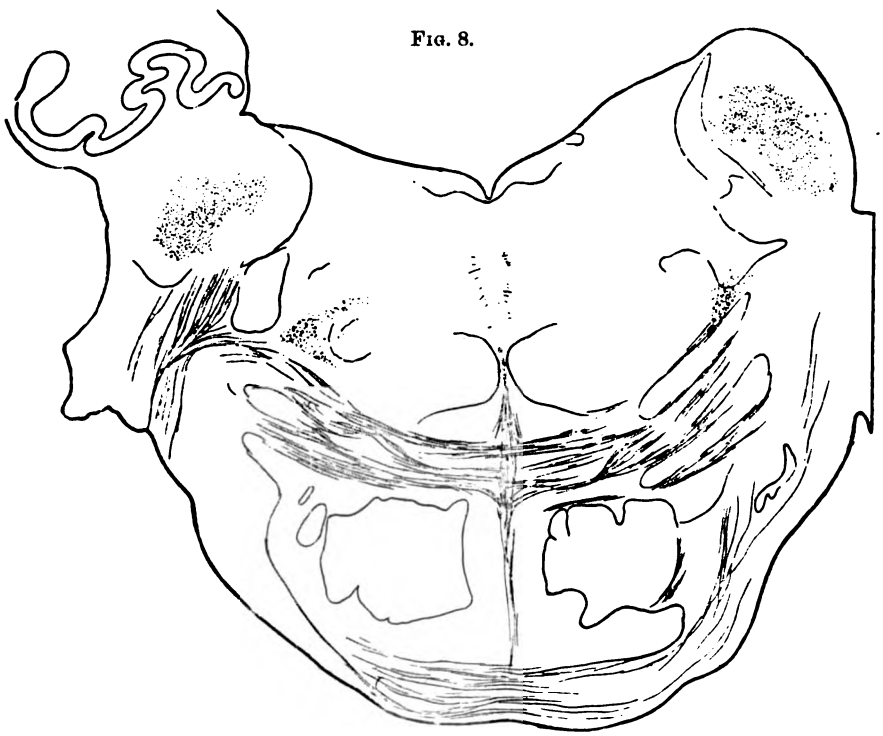
degenerations produced in monkeys failed to find degenerated fibres above the posterior column nuclei.

(*e*) *Ascending degeneration of antero-lateral columns.*

1. *Dorso-lateral, or direct, cerebellar tract.*—At the fifth cervical segment this forms a flat narrow strip at the periphery of the dorsal part of the lateral column. Its anterior margin

FIG. 8.



Level of facial nerve; ascending degeneration.

abuts closely on the adjacent ascending antero-lateral tract, which is also degenerated. At the level of the pyramidal decussation the dorso-lateral cerebellar tract comes to form a somewhat wedge-shaped area occupying the angle between the substantia gelatinosa and the lateral surface of the cord (*see* Figs. 12 and 13). As we trace it higher, its fibres recede still farther

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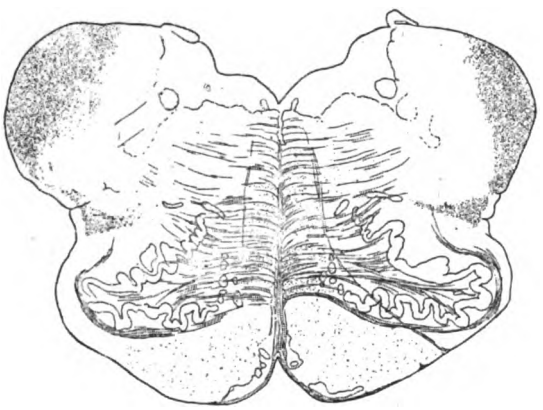
dorsally and run external to the substantia gelatinosa to enter the corpus restiforme and go to the cerebellum (*see* Figs. 5 to 11).

2. *Ascending antero-lateral tract* (*Gowers*).—The head of the

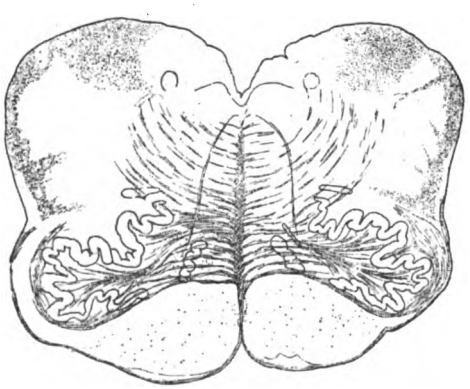
FIG. 9.



Medulla, upper; ascending degeneration.

"comma," situated dorsally, close to the previous tract, from which it is not sharply marked off, is seen at the level of the

FIG. 10.



Medulla, middle; ascending degeneration.

fifth cervical segment to be in apposition to the surface of the cord, whilst its anterior end or tail is spread out diffusely and does not cling so closely to the surface. It extends ventrally in

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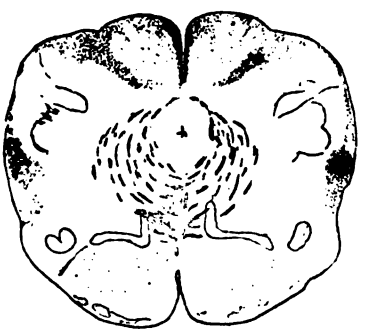
amongst the anterior nerve-roots, and its precise anterior limit cannot be defined owing to the existence of degenerated fibres in the ventral pyramidal tract (*see* p. 16). On tracing Gowers's tract upwards through the medulla, it runs ventral to the

FIG. 11.



Medulla, lower; ascending degeneration.

dorso-lateral cerebellar tract, and when the latter enters the restiform body, Gowers's tract remains at the surface as a triangular mass with its base at the side of the medulla and its apex pointing inwards towards the posterior border of the

FIG. 12.

Pyramidal decussation, upper part; ascending degeneration.

inferior olive, where it becomes somewhat teased out (*see* Fig. 9) In the pons, at the level of the fifth nerve, the tract sinks inwards and lies internal to the trigeminus. It runs ventral to the seventh nerve and dorsal to the fibres of the middle peduncle, and

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sweeps outwards again to run upwards in the lateral fillet external to the superior cerebellar peduncle. In the lateral fillet its fibres are not scattered diffusely all over, but occupy the central part of that area, leaving a clear undegenerated space both to the outer and inner sides. From the lateral fillet its fibres can be traced to the valve of Vieussens, where the fibres of the tracts of the two sides are seen to intermingle (*see* Fig. 5). Sections through the posterior corpora quadrigemina show a few fibres in the region of the lateral fillet, diffusely scattered through the latter. The regions of the anterior corpora quadrigemina and the parts at a higher level were not obtained for examination.

So far as our results go, they are in accordance with those obtained by Hoche (15), von Sölder (30), Patrick (23), and Woro-

FIG. 13.

Pyramidal decussation, lower part; ascending degeneration.

tynski (33), who trace Gowers's tract through the corpus trapezoideum to the region of the corpora quadrigemina. Its further course, whether, as stated by Mott, bending in a loop backwards to stream into the cerebellum, or, as Henneberg (14) maintains, sending a few of its fibres to end in the ventro-posterior part of the lateral nucleus of the optic thalamus, the main mass meantime turning back into the cerebellum, could not be studied in our case.

3. *Pyramidal tracts, ventral and lateral.*—Although, in a section at the level of the fifth cervical segment, the ventral and lateral pyramidal tracts appear sharply mapped out by their relatively scanty degeneration when contrasted with the marked degeneration of the remainder of the antero-lateral columns, yet on close examination they are found not to have escaped

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DESCRIPTION OF PLATE I.

Illustrating the communication by Dr. Purves Stewart on "Spinal Degeneration." (P. 1.)

Ascending degeneration, as seen bilaterally in the following tracts after a lesion at the seventh cervical segment:

Posterior columns.
Direct cerebellar tract.
Ascending antero-lateral tract of Gowers.
Pyramidal tracts, ventral and lateral.

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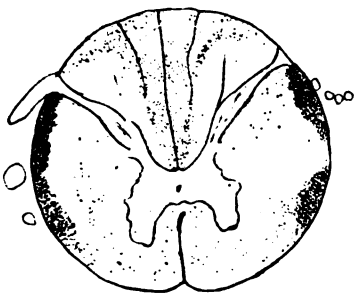

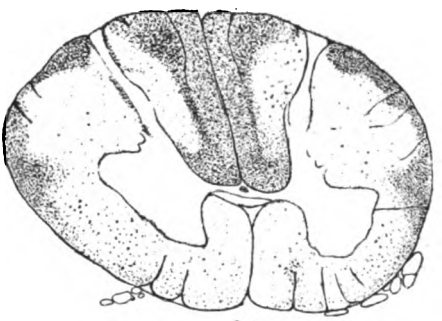

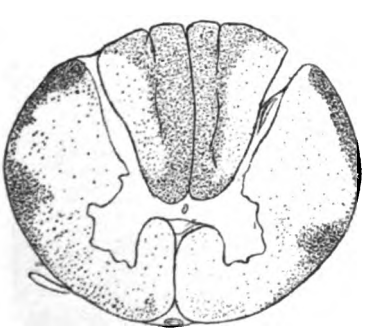

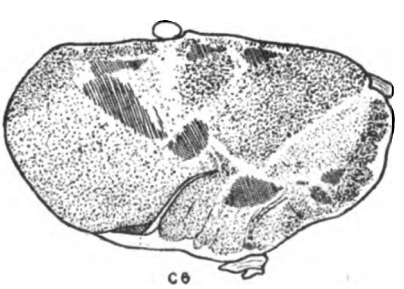

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DESCRIPTION OF PLATE III.

Illustrating the communication by Dr. Purves Stewart on "Spinal Degeneration." (P. 1.)

Descending degeneration, as seen bilaterally in the following tracts:

- Lateral pyramidal tract, as far as the coccygeal segment.
- "Tract X," in seventh and eighth cervical segments; ventro-external to the lateral pyramidal tract.
- Ventral pyramidal tract, as far as the fourth sacral segment.
- Efferent ventro-lateral tract, as far as the fourth sacral segment.
- Fibres in anterior commissure in seventh and eighth cervical and first thoracic segment.
- Posterior column:
  - (*a*) Comma tract of Schultze, as far as ninth thoracic segment.
  - (*b*) Septo-marginal tract (tenth thoracic to second lumbar segment).
  - (*c*) Oval field (third lumbar to second sacral segment).
  - (*d*) Triangle median (third sacral to coccygeal segment).
- Short descending fibres in posterior columns near median septum, in seventh and eighth cervical segments.

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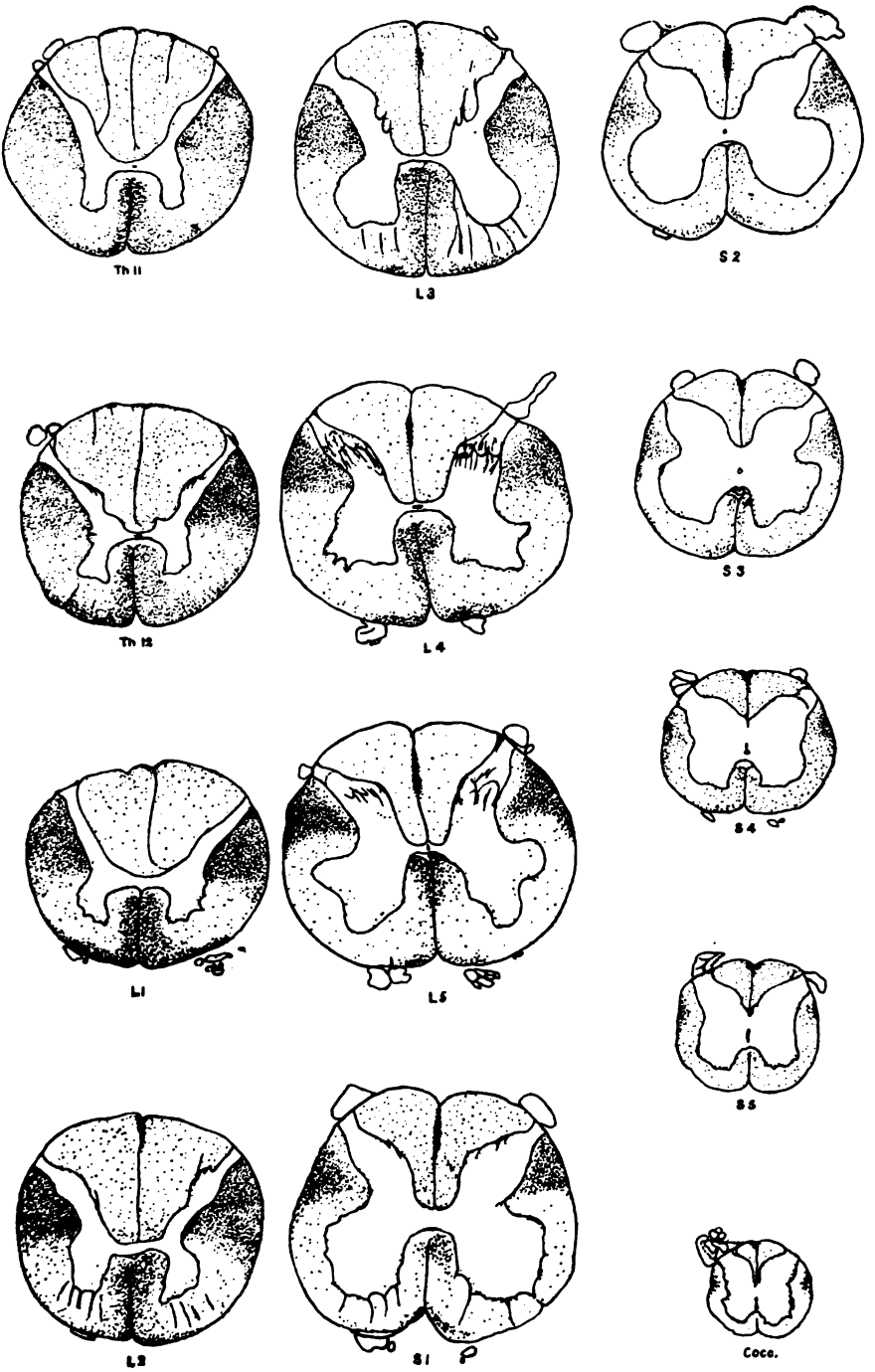

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entirely. As we trace them to higher levels, distinctly degenerated fibres, although scanty and diffusely scattered, can still be detected throughout the pyramidal tracts in the cord, medulla, and pons, *above* the level of the cervical lesion. (*See* Pl. I, also Figs. 9 to 12.)

Whether this degeneration extends up to the motor cortex it is unfortunately impossible to state, since the structures above the pons are not available for examination. The question as to whether this degeneration is an "ascending" or a "descending" one is, for the same reason, impossible of determination, for although on the one hand it might be that it is an "ascending" one, due to the spinal lesion, yet it is also conceivable that at the time of the accident a few of the cortical motor cells might have suffered, producing a descending degeneration in the pyramidal system. At the same time it should be remarked that there was no clinical evidence of such cortical injury. Even within a few hours of the accident, the patient showed neither mental impairment nor weakness of muscles above the level of the lesion.

Conclusions.

The following are the chief conclusions drawn from the study of this case:

1. There is a descending tract, "tract X," in the cervical region, situated ventro-external to the crossed pyramidal tract, separated from the latter by a distinct interval at a plane corresponding to the tip of the lateral horn of the grey matter. It does not extend below the level of the eighth cervical segment. It somewhat resembles in shape, but differs in position, from the tract described by Helweg and v. Bechterew.

2. The fibres of the lateral pyramidal tract, after a lesion in the cervical region, degenerate to the most caudal extremity of the cord.

3. The ventral pyramidal tract extends as a distinct bundle to the fourth sacral segment, below which level its fibres become diffused throughout the anterior columns and are traceable to the most caudal extremity of the cord.

4. The efferent ventro-lateral tract extends downwards as far as the fourth sacral segment. Below this level its fibres

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become diffused over the antero-lateral column. Those fibres which lie nearest to the anterior median fissure extend as a distinct tract further caudally than the outer fibres.

5. Degenerated fibres occur in the white commissure for three segments below a lesion in the lower cervical region.

6. Descending degeneration in the posterior columns occurs in the "comma" tract of Schultze as far down as the ninth thoracic segment. Below that level degeneration continues successively in the "septo-marginal" tract of Bruce and Muir (tenth thoracic to second lumbar), in the "oval field" of Flechsig (third lumbar to second sacral), and in the "triangle médian" of Gombault and Philippe (third sacral to caudal extremity). No demarcation can be traced between the fibres of the "comma" tract of Schultze and those in the other three descending tracts further down in the posterior columns. It is therefore probable that they all form one long combined system.

7. Ascending degeneration of the posterior columns above the level of a cervical lesion does not stop abruptly at the posterior column nuclei. Some degenerated fibres run on both in the internal arcuate and in the postero-external arcuate paths.

8. The ascending antero-lateral tract of Gowers extends upwards through the lateral fillet through the superior medullary velum (where it mingles with the fibres of the opposite side) to the posterior corpora quadrigemina. In the lateral fillet the fibres of Gowers's tract occupy the central part of that structure and do not extend to the margins, either externally or internally.

9. Degeneration also occurs in the pyramidal tracts in the cord, medulla, and pons above the level of the cervical lesion. Whether the degeneration be a true ascending one or not it is impossible to determine from this case.

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July 6th, 1901.

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2. *The immunisation of cattle against* Bacillus tuberculosis.

By J. McFadyean.

I PROPOSE to bring before the Society the results of some experiments in which an attempt was made to immunise animals of the bovine species against tuberculosis.[1] As a matter of fact, the object in view at the outset of the earliest of the experiments was not to immunise, but to make observations regarding the earliest date at which an animal will react to tuberculin after infection with tubercle bacilli.

To this end cattle were infected by intravenous injection of virulent tubercle bacilli, and afterwards, at intervals, tested with tuberculin. It was pretty confidently expected that the ultimate and not very long deferred result of such experiments would be the death of the animals from tuberculosis, and when very large doses of virulent bacilli were used that was what actually happened. In some instances, however, the experimental animals never developed any decided symptoms of infection, and gradually ceased to react to tuberculin. This, of course, might have been the result of a sufficient degree of natural immunity, or it might have been brought about by a curative property of tuberculin. In either case the result raised the question whether the animal's natural powers of resistance had been increased during its recovery from the experimental infection, and suggested a repetition of the infection with large doses of bacilli. It also suggested the employment of repeated injections of tuberculin with the object of curing and immunising animals

[1] The cost of the investigation was defrayed by a grant from the Royal Agricultural Society of England.

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that had contracted tuberculosis naturally. The experiments, unfortunately, are too few, and as will presently appear, the circumstances in some of them are too complex to justify one in offering a very confident explanation of the results, but they are at least interesting as showing that cattle may have conferred on them a very high degree of immunity against tuberculosis.

Case 1.—The subject in this case was a yearling shorthorn heifer purchased on September 30th, 1899. It was first tested with tuberculin on October 9th, and it reacted distinctly, the temperature rising to 106° at the twelfth hour. The test was repeated on the 12th of the same month, and it again reacted, the maximum temperature recorded being 106·2° (at the twelfth hour). Subsequent tests with the same quantity of tuberculin (1 c.c.) were made as shown below:

Date.	Max. Temp.
Oct. 24	103·4°
„ 26	105·6
Nov. 1	102·2
„ 10	104·5
„ 21	103·3
„ 28	102·6
Dec. 9	102

It was decided to use larger doses of tuberculin with a curative object, and the particulars of these injections were as follows:

Date.	Dose.	Max. Temp.
Dec. 22, 1899	10 c.c.	100·6°
„ 26, „	10 „	102
„ 28, „	10 „	102·6
Jan. 1, 1900	10 „	102·1
„ 10, „	20 „	102·3
„ 13, „	20 „	102
„ 17, „	20 „	102
„ 21, „	20 „	102
„ 24, „	20 „	101

On February 6th 2 c.c. of a liquid that was very rich in

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tubercle bacilli was injected into one of the jugular veins of the animal. The liquid was prepared by rubbing up some caseo-purulent matter from the mesenteric gland of a horse with sterile water. On the same day two other animals of about the same size and age were infected in the same way with the same quantity of the same material. It is unnecessary to refer further to these two animals except to say that they subsequently became ill, and when they were killed on April 10th their lungs were found to contain numerous tubercles, while the bronchial and mediastinal lymphatic glands were greatly enlarged and caseated. On February 14th and 17th the animal, which had previously failed to react even with 20 c.c. of tuberculin, reacted distinctly to the test with 1 c.c. Between February 24th and March 28th it was treated with doses varying from 5 c.c. to 20 c.c., and on none of these occasions was there any important rise of temperature after the injection. After the last-mentioned date it was left untreated, and on May 22nd following it was killed. A most searching *post-mortem* examination revealed no lesion anywhere except in one mesenteric gland, which contained a completely calcified tubercle about the size of a pea. It appears to be fair to assume that this lesion had been in an active condition when the animal was purchased, and that it was accountable for the reactions at first obtained.

It is impossible to doubt that this animal had latterly a very high degree of immunity against tuberculosis, since the intravenous injection of a large quantity of virulent tubercle bacilli caused it no apparent inconvenience, and entirely failed to set up any permanent lesion in the lung or elsewhere. It is conceivable, but very improbable, that the animal had a high degree of natural immunity; the fact that it had contracted the disease naturally is against that view. It appears to be much more likely that the immunity was acquired while the animal was under experiment, but it is not possible to say with any confidence whether the credit of this should be ascribed to an immunising effect of the tuberculous lesion in the mesenteric gland or to the injections of tuberculin. Possibly both of these may have been factors in the production of the immunity.

Case 2.—This animal has had a history very similar to that just described. It is an Ayrshire heifer, which was about a year

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and a half old when it was purchased on September 30th, 1899. It was tested with tuberculin on October 9th and 12th, and it reacted distinctly on both occasions. On November 27th following it was again tested, and the temperature rose from 101·1° to 103° (ninth hour). On January 8th, 1900, it was tested for a fourth time, and the maximum temperature during the following fifteen hours was 106°. On each of these occasions the dose of tuberculin injected was 1 c.c.

On January 11th 1½ c.c. of a liquid rich in tubercle bacilli was injected into one of the animal's jugular veins. The liquid was prepared by rubbing up a portion of the tuberculous liver of a rabbit with sterile bouillon and allowing the coarser particles to settle. The rabbit had been inoculated intravenously on December 6th with tubercle bacilli from a caseous bronchial gland of an ox, and its liver was crammed with miliary tubercles. On the same date (January 11th) another heifer of about the same size and age was made the subject of a parallel experiment. This control animal was killed on March 2nd following, when it was very ill, and the *post-mortem* examination revealed a dense miliary tuberculosis of the lungs.

The other heifer was treated with tuberculin in 20 c.c. doses on January 15th, 17th, 21st, and 24th, February 28th, and March 8th, and on none of these occasions was there any rise of temperature amounting to a reaction. On March 15th it received 10 c.c., and on March 28th 20 c.c., again without any distinct reaction.

On April 5th, 1900, the heifer was again inoculated intravenously with tubercle bacilli. The material for inoculation was in this instance prepared by triturating a portion of the fresh lung of a rabbit dead from tuberculosis (as the result of an intravenous inoculation) with sterile water, and allowing the coarser particles to settle. A cover-glass preparation made from the liquid showed numerous tubercle bacilli, and the quantity of the liquid used for the inoculation was 2 c.c. The material employed for the inoculation of the before-mentioned rabbit was taken from the tuberculous pharyngeal gland of an ox.

The intravenous injection did not occasion any recognisable disturbance either at the time or afterwards, but the heifer reacted distinctly to an ordinary dose of tuberculin when tested

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on June 13th, July 18th, and October 16th following. On the last of these occasions the temperature rose from 101° to 105·4° (at the fifteenth hour). The test was repeated on November 20th, when there was an indecisive rise of temperature.

On November 28th, 1900, a third intravenous injection of tubercle bacilli was administered to the heifer. The liquid for inoculation was prepared by triturating a quantity of caseo-purulent matter from the tuberculous spleen of a horse with sterile water, and allowing the coarser particles to settle. The quantity of the supernatant liquid injected into the heifer was 2 c.c., and a cover-glass preparation made from it showed that it was very rich in tubercle bacilli. As a control experiment a rabbit was inoculated intravenously with two drops of the same liquid, and it died on April 12th, 1901, with numerous tubercles in its lungs and kidneys. The heifer was tested with tuberculin on December 19th following, with the result shown below:

Time of Injection.	6th Hour.	9th Hour.	12th Hour.
102°	105° ...	104·2° ...	102·6°

An almost identical reaction was obtained when the test was repeated on January 22nd.

On January 30th last the heifer was again inoculated intravenously, 5 c.c. of a rich emulsion of tubercle bacilli (from an artificial culture) in sterile bouillon being injected into the right jugular vein. At the same time a control cow was similarly inoculated with 5 c.c. of the same emulsion. Some of the emulsion was further diluted with five volumes of sterile bouillon and ½ c.c. of the diluted liquid was injected into the auricular vein of a rabbit.

The control cow was killed seventeen days after inoculation (February 16th) as it was then unable to rise on account of weakness and emaciation due to parasitic gastritis, from which the animal had been suffering for some months previously. At the *post-mortem* examination it was not possible to detect with the naked eye any tubercles in the lungs or elsewhere, but scrapings from the lung parenchyma and from the bronchial glands showed tubercle bacilli. Microscopic examination of sections of lung-tissue prepared after hardening in alcohol showed that the parenchyma was crammed with minute tubercles, all of which contained numerous tubercle bacilli

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scattered through them. Giant-cells were already formed in some of the tubercles. The distribution of the bacilli in the tubercles, and their presence at such an early period in the bronchial glands, are conclusive evidence that the bacilli employed for the inoculation were both living and virulent.

The rabbit died on March 1st, and the *post-mortem* examination revealed a dense crop of miliary tubercles in the lungs, liver, and spleen, and a few tubercles in the kidneys.

On the day following the intravenous injection the heifer's temperature had risen to 104·2°, and it remained at about that level till February 4th, when it had fallen to 99·6°.

During the following three months the heifer appeared to be in good health, and its general condition remained good. On May 15th it was tested with an ordinary dose of tuberculin, and the maximum temperature recorded during the following fifteen hours was 102·8° (original 102°).

On May 18th the heifer was again inoculated intravenously with 5 c.c. of a rich emulsion of an artificial culture of virulent tubercle bacilli. On the previous day six guinea-pigs had been inoculated intraperitoneally with ½ c.c. of a considerably thinner emulsion from the same flask of artificial culture.

One of these died from tuberculosis in three weeks, and when the others were killed on June 14th, they were all found to be extensively tuberculous.

On the evening of May 18th the heifer's temperature was found to have risen from the normal (101° on the 17th) to 105·6°, but it gradually fell, and had returned to the normal on May 21st. Between the latter date and June 18th it never reached 102°. On June 18th the animal was tested with an ordinary dose of tuberculin, with the result shown below:

Time of Injection.	6th Hour.	9th Hour.	12th Hour.
101·6° ...	103° ...	102° ...	101·4°

The experimental heifer was inoculated a sixth time on July 31st last. The material employed was an artificial culture of tubercle bacilli rubbed up with sterile water, so as to form a turbid liquid. A cover-glass preparation made with a trace of this liquid showed numerous tubercle bacilli, both singly and in clumps. The quantity of this liquid injected into the heifer's jugular vein was 5 c.c.

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At the same time two guinea-pigs were each inoculated simultaneously with $\frac{1}{10}$ c.c. of the same liquid. One of the guinea-pigs died on August 26th (twenty-six days) and the other on September 3rd (thirty-four days) from a generalised tuberculosis.

On the evening of July 31st, six hours after the intravenous inoculation, the heifer's temperature was 103·3°, but on the following day it had fallen to 100·8°, and the animal did not exhibit any abnormal symptoms during the following two months. It was tested once during that period (September 13th), and it did not react (maximum temperature 103·2°).

On October 24th last the heifer was inoculated a seventh time. On this occasion 10 c.c. of a liquid rich in tubercle bacilli was injected into one of the jugular veins. The liquid was prepared by rubbing up a quantity of the rich surface growth from a bouillon culture of tubercle bacilli with sterile bouillon, and the number of bacilli present may be inferred from the fact that the liquid was opaque in a test-tube one inch in diameter.

At the same time two guinea-pigs were inoculated intraperitoneally with $\frac{1}{10}$ c.c. of the same liquid, and a control calf (eight months old) and a pony were inoculated intravenously, the former receiving 2 c.c., and the latter 3 c.c. of the liquid. Both of these animals had been tested with tuberculin on October 22nd, and had not reacted.

Four hours after inoculation the heifer's temperature had risen from 102·2° to 106·2°, and during the next ten days it fluctuated between 102·8° and 104°. Since the 4th inst. it has never reached 103°. It was tested with tuberculin on November 7th, and did not react (maximum temperature 102·2°).

One of the above guinea-pigs was killed yesterday (November 18th), and the *post-mortem* examination showed a caseous nodule where the needle had penetrated the abdominal wall, and numerous tubercles, already macroscopic, in the spleen and omentum.

The young bull inoculated as a control animal on October 24th is still alive. On the two days preceding the inoculation its temperature varied from 103° to 104°, and the injection into the veins did not cause any notable rise. Between October 25th and November 6th the temperature was generally

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normal. The bull was tested with tuberculin on November 7th, and it reacted as follows:

Time of Injection.	6th Hour.	9th Hour.	12th Hour.	15th Hour.
102·5° ...	102·8° ...	103° ...	104·6° ...	104·8°.

During the following week the temperature fluctuated between 103° and 105·2°. On the 14th it rose to 106°, and since that it has never fallen as low as 104°. Prior to, and for a few days after, inoculation, the respirations numbered about twenty per minute. Since then they have become more frequent, and are now over thirty.

Immediately before the intravenous inoculation the control pony had a temperature of 99·7°, and three and a half hours afterwards it had risen to 101·8°. Subsequently the temperature was generally normal, but the respirations gradually increased in frequency during the last ten days, and this forenoon they numbered forty per minute. The pony was tested with tuberculin on November 7th, and it reacted as follows:

Time of Injection.	6th Hour.	9th Hour.	12th Hour.	15th Hour.
100·5° ...	101·4° ...	104° ...	103·1° ...	102·2°

With the object of exhibiting the animal's lungs to the Society, I had it killed to-day. The *post-mortem* examination showed a miliary tuberculosis of a density that is seldom or never seen in natural cases. In the collapsed lung the tubercles, which are quite macroscopic, bulk more largely than the remnant of normal lung-tissue. I have hurriedly prepared some sections which show that the tubercles contain a considerable number of giant-cells, and that some of them have already undergone central necrosis. Tubercle bacilli are present in considerable numbers, especially in the necrotic centres. [Hand specimen and sections of lungs exhibited.]

The bronchial glands were about double the normal size, but tubercles were not visible in them with the naked eye, and no tubercle bacilli were detected in a scraping from the gland tissue. The abdominal organs appeared to be quite normal, and no tubercles were visible in the spleen or liver, and only a very few doubtful points in the kidneys.

I very reluctantly sacrificed this pony, but I was anxious to exhibit to the members of the Society the condition of lung set

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up in a non-immunised animal by these intravenous injections of tubercle bacilli. It ought to be remembered that this pony was about the same size as the immunised cattle (with one exception), and whereas the former received only 3 c.c. of the liquid containing tubercle bacilli, two of the experimental cattle on the same day received 10 c.c. of the same material. Moreover, one of them (Case 3) had received a similar amount of bacilli on October 5th last.

Case 3.—The subject of this experiment is a Hereford heifer, now three years old. It was first tested with tuberculin on May 5th, 1899, and there was then an entire absence of reaction.

On May 10th, 1899, the animal, then about a year old, was inoculated intravenously with 2½ c.c. of a liquid rich in tubercle bacilli. The bacilli were obtained from the tuberculous liver of a pheasant which had contracted the disease naturally. A cover-glass preparation made with a trace of the liquid used for inoculation showed tubercle bacilli in every field of the microscope. The animal was tested with tuberculin on May 11th and 20th, and on these occasions there was no reaction. The test was repeated on May 31st with the following result:

Time of Injection.	6th Hour.	9th Hour.	12th Hour.	15th Hour.
102·8°	103·8°	104·4°	106°	105°

There was thus a distinct reaction to the tuberculin test on the twenty-first day after injection. It was then resolved to repeat the test at short intervals. The following table shows the results of successive tests:

Date.	Time of Injection.	6th Hour.	9th Hour.	12th Hour.	15th Hour.
June 13	101°	102·8°	105°	105·6°	105°
„ 22	102·8	103·4	104	104·8	104
„ 29	101·4	103	104·2	105	105
July 7	102·4	103	104	104·8	104·4
„ 15	101·4	103·2	104	104	103·8
„ 22	102	104	102·8	102·5	102·4
Aug. 4	101·4	103·6	103·8	104	103·2
„ 11	101·9	102·7	104·6	101·4	100·8
„ 18	103	103·3	103·3	102·9	103
„ 25	102	102·9	103·4	103·1	101·6
Sept. 1	101·5	103	103	102·5	101·3
„ 8	103·2	103·8	103·6	102·2	102
„ 16	102	103·5	103·6	103	102·2
„ 24	101	103·4	102·6	101·8	101·2
Oct. 26	102	101·4	102	101·9	101·8

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On November 11th the heifer was again inoculated intravenously, this time with 2½ c.c. of liquid containing tubercle bacilli from the liver of a rabbit. The rabbit had died twenty-six days after intravenous inoculation with material from a tuberculous mesenteric gland of a horse, and its liver was crammed with miliary tubercles which were very rich in tubercle bacilli.

The heifer was tested with an ordinary dose of tuberculin on November 21st and 28th, and there was no reaction. The test was repeated on the dates and with the results shown below:

Date.	Time of Injection.	6th Hour.	9th Hour.	12th Hour.	15th Hour.
Nov. 21	103°	102°	101°	101°	100·4°
„ 28	102	103·4	101	102·4	102·4
Dec. 9	101·3	102	101·4	101	100·6
„ 22	101·7	101·7	101·9	102	101·2
Jan. 8	101	102·6	102	101·5	102

On January 11th, 1900, the heifer was inoculated intravenously for the third time, 1½ c.c. of a liquid containing tubercle bacilli (same as used on that date for the subject of Case 2) being injected into one of the animal's jugular veins. As in the previous cases, the injection did not occasion any obvious disturbance, and the animal remained in apparent good health.

On April 5th a fourth intravenous injection of tubercle bacilli was given. The liquid injected was the same as that used on the same date for the subject of Case 2, but the quantity injected was 3 c.c. No symptoms of illness followed the operation, but when the animal was tested with tuberculin on June 13th, July 18th, and October 16th following it reacted distinctly.

November 20th was the date of the next test, and on that occasion there was no reaction, as shown below:

Time of Injection.	6th Hour.	9th Hour.	12th Hour.	15th Hour.
101·2°	101·5°	101·8°	101·8°	101·4°

On November 28th, 1900, the heifer was inoculated intravenously for the fifth time. The material employed was the same as that used on the same date for the subject of Case 2, and the quantity of liquid injected was the same, viz. 2 c.c. On November 29th the animal's temperature was 101·6°, and

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during the next three weeks it never exceeded 102°. On December 7th the heifer was tested with tuberculin, and the result was as follows:

Time of Injection.	9th Hour.	12th Hour.	15th Hour.
101·4° ...	101·8° ..	102·6° ...	102°

The test was repeated on December 19th and January 22nd, and there was an entire absence of reaction. On January 30th of this year a sixth intravenous injection of tubercle bacilli was administered, the material and the dose being the same as was used in the previous case on that date. On the same evening the temperature had risen from 102° to 104·2°, and it remained over 104° during the next four days. On February 5th it had fallen to 102°, and subsequently it remained about the normal. The animal was tested with tuberculin on February 12th, and the result was as follows:

Time of Injection.	9th Hour.	12th Hour.	15th Hour.
101° ...	102·4° ...	101·2° ...	101°

On March 23rd last the heifer was inoculated intravenously for the seventh time. In this instance the material for injection was prepared by taking a quantity of the surface growth from a bouillon culture of the tubercle bacillus and rubbing it up with sterile water. The liquid was decanted into a test-tube, and the coarser clumps of bacilli were allowed to deposit. The supernatant liquid was still distinctly hazy from suspended bacilli, and the quantity of it injected into the heifer's jugular vein was 15 c.c. As a control experiment a rabbit was inoculated intravenously with two drops of the same liquid. The rabbit was killed on April 25th, and its lungs were then found to contain numerous pin-head tubercles in which tubercle bacilli were abundantly present.

On the evening of March 23rd the heifer's temperature had risen from the normal to 105·4°. On the 24th it was 103°, and on the following day it had fallen to about normal (102°). The animal continued in apparent health, and when it was tested with tuberculin on May 15th the maximum temperature was 102·8° (sixth hour).

On May 18th last the heifer received an eighth intravenous injection of tubercle bacilli. The material and dose were the

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same as in the preceding case on the same date. On the evening of May 18th the temperature had risen to 105·6°, but on the 20th it had returned to the normal. On June 17th it was 102°, and on the following day when the animal was tested with tuberculin there was no distinct reaction, the maximum temperature recorded during the following fifteen hours being 103° (sixth hour).

On July 21st last, the heifer received a ninth intravenous injection of tubercle bacilli, the material and the dose being the same as for the animal of last experiment on the same date, viz. 5 c.c. of a rich emulsion of tubercle bacilli from an artificial culture. Six hours afterwards the heifer's temperature had risen to 105·7°, and it remained above normal for about a week afterwards. On September 13th the animal was tested with tuberculin, and the result was indecisive, the temperature rising from 101·7° to 104·6° at the ninth hour, but falling to 101° at the fifteenth hour.

On October 5th last the heifer received a tenth intravenous inoculation of tubercle bacilli. The material was prepared by rubbing up part of the surface growth of an artificial bouillon culture with sterile water and the quantity of liquid injected was 10 c.c. The liquid was opaque in a test-tube one inch in diameter, and a cover-glass preparation made from it showed great numbers of bacilli in every field. At the same time two guinea-pigs were inoculated subcutaneously with ½ c.c. of the liquid, after dilution with ten volumes of sterile water.

One of these guinea-pigs was killed on November 17th, and the *post-mortem* examination showed a caseating lesion in the abdominal wall at the seat of inoculation, enlargement and caseation of the adjacent precrural gland, and numerous tubercles in the spleen, liver, and lungs.

Three hours after inoculation the heifer's temperature had risen to 105·4°, and during the next four days it fluctuated between 101·7° and 103·2°. After that it became normal (under 103°), and when the animal was tested with tuberculin on October 22nd it did not react.

On October 24th the heifer was inoculated intravenously for the eleventh time. The details of the inoculation were exactly the same as for the subject of the preceding experiment

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on the same date (10 c.c. of a rich emulsion of tubercle bacilli from an artificial culture). Just before inoculation the temperature was 102·2°, and four hours afterwards it had risen to 107·4°. On the following day it had fallen to 103·1°. Since November 3rd the temperature has only once touched 103°. Since the date of the last inoculation the respirations have been abnormally frequent, but they are now declining, and the animal's appetite and general appearance are undisturbed.

Case 4.—It may suffice if the particulars relating to this case are given in a less detailed form. The animal is a shorthorn cow, now about six years old. It was tested with tuberculin on September 19th, 1898, and there was no reaction. On the 29th of the same month it was inoculated intravenously with 4 c.c. of sterile water holding in suspension tubercle bacilli from the liver of a fowl (natural case of the disease). Microscopic examination showed that the liquid was rich in tubercle bacilli.

The cow was tested with tuberculin on October 7th following, and the result was as shown below:

Time of Injection.	8th Hour.	10th Hour.	12th Hour.	14th Hour.
101·8° ...	105° ...	105·4° ...	105·4° ...	105°

There was an equally pronounced reaction when the test was repeated on October 17th and November 18th, but the animal failed to react when tested on December 15th. Since that date it has been reinoculated intravenously with tubercle bacilli as follows:

November 11th, 1899, with 4 c.c. of the liquid used on that date for Case 3.

April 5th, 1900, with 3 c.c. of the same liquid as was used on that date for Cases 2 and 3.

March 23rd, 1901, with 15 c.c. of the liquid used on the same date for Case 3.

May 18th, 1901, with 5 c.c. of the same liquid as was used on that date for Cases 2 and 3.

July 31st, 1901, with 5 c.c. of the same liquid as was used on that date for Cases 2 and 3.

October 5th, 1901, with 10 c.c. of the liquid used on that same date for Case 3.

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The cow was tested with tuberculin on October 22nd last, and did not react. At the present time the animal is very fat, and it appears to be in perfect health.

It seems certain that the three surviving animals have now a very high degree of immunity against tubercle bacilli, since they are able to bear intravenous inoculations with very large numbers of these without serious disturbance. It must be noted that none of the inoculations were made with human tubercle bacilli. Except in the first inoculation in Cases 3 and 4, in which avian tubercle bacilli were injected, the bacilli employed were either those found in lesions of natural or experimental tuberculosis of the lower animals, or artificial cultures obtained from such animals. In all cases the bacilli were proved by control experiments to be highly virulent for small rodents, and in some cases for control cattle as well.

The question may now be asked: Are the results attributable to a high natural immunity of the experimental animals, or to an immunising effect of the treatment to which they were subjected? Putting aside the evidence afforded by the control experiments with cattle, it scarcely seems open to doubt that the immunity is now far higher that it was originally. The degree of natural immunity against tuberculosis possessed by cattle varies a good deal from individual to individual, and probably it is sometimes so strong that it would enable an animal to resist inoculation with a moderate number of virulent bacilli; but nothing that is known makes it at all likely that any bovine animal is naturally so immune that it could resist inoculation with the colossal number of virulent bacilli that were used in some of these experiments; and even if it were held that some individuals of that kind do exist, it is not reasonable to suppose that four animals selected at random for my experiments all possessed this very high degree of natural immunity.

Assuming, therefore, that these cattle have actually been immunised against tubercle bacilli, the next question to present itself is: What was the mechanism by which the immunity was brought about? Was it the tuberculin or the interaction between the bacilli and the animal cells? In Cases 1 and 2 the first intravenous inoculation was made with a very large number of virulent mammalian bacilli—such a number as would

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almost certainly have caused the death of any ordinary animal, and yet no serious effect was produced. But both these animals had previously been treated with tuberculin, and both were the subjects of naturally contracted tuberculosis before the treatment was begun. Probably in these cases the immunity which the animals had acquired at the time of their first inoculation was due to their previous reactions to tuberculin, and since then it has been greatly strengthened by the later intravenous inoculations.

In the other animals (Cases 3 and 4) the first inoculation was made with avian tubercle bacilli, which are well known to have a feeble virulence for mammals. Nevertheless the animals became affected, as proved by their reaction to tuberculin, and it is probable that the interaction between these bacilli and the animal cells, aided by the tuberculin injections, left them with higher powers of resistance than they originally possessed. Each of the subsequent inoculations, involving the interaction between the animal cells and a large number of virulent bacilli, have probably strengthened the immunity.

It will be remembered that Professor Koch was led to the idea which suggested the preparation of the new tuberculin (TR) by observing what he took to be evidence of a process of immunisation during the course of attacks of miliary tuberculosis. He interpreted the poverty of the tubercles in bacilli in some of these cases to increased powers of resistance acquired by the animal during the evolution of the tubercles, and surmised that artificial immunisation might be brought about by the subcutaneous administration of mechanically destroyed and disintegrated, but chemically unaltered, tubercle bacilli. I know of only one instance in which an attempt was made to immunise cattle in this way. The experiment was carried out by Professor Bang, of Copenhagen, and it was mentioned by him in a paper which he read before the recent British Congress on Tuberculosis. The attempt entirely failed, although each calf received 128 c.c. of TR.

In conclusion, it is perhaps well to say that I do not suggest that immunisation of cattle for practical purposes is possible by the methods employed in the experiments I have described. In this connection I am reminded of the mathematician who is said to have thanked God that he had discovered a fact

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which could never be put to any practical purpose. The practical, as opposed to the experimental, immunisation of cattle or other animals against tuberculosis may be impossible by this or any other method, but at the same time I venture to hope that the facts I have brought before the Society will not be thought entirely devoid of interest. *November 19th*, 1901.

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3. *A note on the methods of conducting hæmolytic experiments.*

By G. F. Petrie,

Research Student, Jenner Institute of Preventive Medicine.

I have had occasion recently during the course of work bearing upon the products of the *Bacillus pyocyaneus* to make a number of experiments relating to the hæmolysins elaborated in the course of its growth. These have been shown, first of all by Bulloch and Hunter, and somewhat later by Weingeroff, to exist in cultures filtered a variable time after the date of inoculation. So far as the scope of my work in this direction has extended, the conclusions arrived at coincide in the main with those of the above-mentioned authors. Thus the resistance of the pyocyanolysin to heat was found in my experiments to be very great. On the other hand, hæmolysis seemed to go on equally well at comparatively low temperatures, *e. g.* exposure at 13° F. for nineteen hours without preliminary incubation at 37° C. as usually recommended. The fluid chiefly used was a Berkefeld filtrate of a culture derived from the laboratory stock culture grown between 20° and 25° C. for four months in the solution recommended by Emmerich and Löw as a suitable medium for the growth of the *B. pyocyaneus*. The medium before inoculation was tested on the blood selected for the experiments, and was found to cause no hæmolysis. Ordinary peptone broth cultures were also employed, and it was observed that no hæmolysis took place until the cultures were incubated for at least a week at 37° C. (this refers, of course, to the filtered cultures).

In carrying out these experiments a considerable amount of

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evidence accumulated to show that hæmolytic tests present a wide margin of possible fallacy in the conclusions arrived at from positive results. It must be remembered that hæmolysis is not a phenomenon dependent only on specific complex bodies found in cultures of various micro-organisms. On the contrary, it is, of course, well known that extremely simple agents, such as distilled water, solutions of certain simple salts, etc., easily bring it about, and that the reaction of the medium has an important influence. The complexity of the constituents entering into the composition of cultures after bacterial growth has gone on for some time makes it extremely difficult to appreciate the exact *rôle* played by each of them in a phenomenon of the nature of hæmolysis, and it is therefore important to complicate the reaction as little as possible. With a view to lessening the risks of misinterpreting positive results it seems preferable to avoid, as far as possible, the use of preservative reagents, especially in cases where a comparative estimate is required of the hæmolysis of several kinds of blood. It is significant that each of the constituents of Ehrlich's reagent—carbolic acid, glycerine, distilled water,—is capable of hæmolysing red corpuscles. I have found that in the proportion recommended (viz. 5 per cent. of the solution to be tested—in this experiment 5 per cent. in isotonic solution) 50 per cent. of the resulting fluid added to an emulsion of blood in isotonic solution caused well-marked hæmolysis, and 20 per cent. distinct hæmolysis of rabbits' red corpuscles. In cases in which the lysin is destroyed by heat, *e. g.* the staphylolysin, a simple control test is provided, but it is otherwise with hæmolysins, such as the pyocyanolysin and typholysin, which seem to possess very great heat-resisting powers. Then again, apart from the composition of the medium in which the corpuscles are immersed, the condition of the cells themselves is a factor which must be taken into account in assessing the value of the results obtained in hæmolytic experiments. Defibrinated blood, if kept even at a fairly low temperature, is liable to undergo autolysis, and short of this the permeability of the red corpuscles is undoubtedly altered. Thus I have found that defibrinated rabbits' blood, if kept for a day or two, showed hæmolysis after nineteen hours at 13° C. in a solution which was isotonic for the same blood in a fresh condition. Stewart's results, recently published, furnish a

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corroborative instance. "There is," he states, "a noteworthy distinction between the perfectly fresh corpuscles and corpuscles which have stood some time in the length of the period of resistance to the entrance of NH_4Cl, which is much greater for fresh than for stale corpuscles." Other reasons for discarding the use of defibrinated blood are to be found in the chances of bacterial contamination, and the difficulty of obtaining fresh defibrinated blood when required. I accordingly use blood obtained fresh from an ear-vein. It was found, however, that if no precautions were observed to prevent clotting the control tubes containing isotonic salt solution showed at the end of nineteen hours distinct hæmolysis. This autolysis may be attributed in great probability to the fibrin carrying down the proteolytic enzyme of the blood, which in some way influences the permeability of the stroma of the cells. To obviate this a solution was made up consisting of 0·1 per cent. Na oxalate and 0·85 per cent. NaCl. The blood on escaping is at once thoroughly mixed with this solution. This procedure proved quite effectual in preventing autolysis of the red corpuscles. Microscopical examination of a hanging drop showed that on the whole the cells preserved their contour with comparatively little variation from the normal—slight crenation of the corpuscles proving that the fluid is, in fact, somewhat hypertonic. It is advisable that the osmotic pressure of the medium should be slightly greater rather than exactly equivalent to that of the corpuscles; the balance of osmotic pressure is then less easily disturbed by adventitious causes. It has been stated, as a matter of fact, that normal human plasma is hypertonic with respect to the red corpuscles. Another point which arises by implication from what has been already stated is the question of the time limit which may be considered a fair one for the exposure of the blood to the hæmolytic agent. I believe that conclusions derived from experiments of a duration of over nineteen or twenty hours are of uncertain value. Careful controls should be simultaneously carried out with isotonic salt solution.

So far as one has read of the methods of conducting these experiments, roughly quantitative tests, varying rather widely in the way they are carried out by different observers, appear to be used. It seems desirable that greater accuracy should be introduced into the procedure adopted, because if one wishes to

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investigate the comparative powers of two or more different fluids containing the same hæmolysin, or if variations in the permeability of different corpuscles be the subject of inquiry, the results are invalidated unless absolutely identical conditions have obtained during the experiments. For this reason it is necessary to add definite percentages of the hæmolytic fluid to the isotonic solution in which the corpuscles are suspended. In the same way equal amounts of blood, measured accurately in a calibrated pipette similar to those used in the various kinds of blood-estimation apparatus, should be added to each test-tube. These must be of equal diameter, in the lower part at least, so that the hæmoglobin diffused in the liquid may be estimated with greater accuracy. The spectroscope may be requisitioned in cases where a slight or doubtful hæmolysis has taken place. Complete sedimentation of the corpuscles by means of a rapidly revolving centrifuge is important, because the Hb bands are given equally by the red cells and by the Hb after it has left the corpuscles. It is obvious, also, that the use of perfectly fresh blood in the manner described will ensure more reliable results for comparative purposes than if specimens of defibrinated blood of different ages be used.

An advantage to be gained by instituting an accurate system of examination in hæmolytic tests is that a method conducted on these lines is easily adaptable for clinical application.

To summarise the steps briefly—

1. Use absolutely fresh unclotted blood.

2. Prepare in test-tubes of equal size known percentages of the hæmolysin in isotonic oxalate solution.

3. Add to each of the tubes exactly the same amount of blood, and mix well.

4. Incubate tubes for the same length of time at 37° C.

5. Centrifugalise till all the corpuscles settle at the bottom of the tube, forming a sharp line of demarcation between the blood and the supernatant liquid.

6. In every experiment have control tubes containing isotonic salt solution alone.

7. In doubtful cases examine microscopically.

November 5th, 1901.

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4. *A case of malignant endocarditis due to* Bacillus coli communis.

By F. W. Andrewes.

Any one who is in the habit of practising the routine bacteriological examination of cases of malignant endocarditis must hail with relief any departure from the ordinary varieties of pyogenic organisms which are so constantly found in them. The number of recorded cases due to infection with *Bacillus coli communis* is comparatively small, so that I am glad to be able to bring before this Society a well-marked and indisputable example of the condition.

The patient was a schoolboy of 12 years, admitted to St. Bartholomew's Hospital under the care of Sir Lauder Brunton in June, 1901. The total duration of his illness was four months, and its onset was insidious, with slight headache and pains in the limbs. There was nothing in the history to indicate the channel of primary infection—nothing pointing to any previous intestinal trouble—nor was any primary lesion ultimately found at the autopsy. He had never suffered from rheumatism, scarlet fever, or other common antecedent of valvular disease, and, as may be seen from the specimen exhibited, there is no chronic thickening of the valves or other sign of pre-existing valvular disease. The case appears to be a primary endocardial infection.

The clinical symptoms and signs were those of malignant endocarditis in a marked form. He had already been ill for two months when he first came under observation, and he was two months in the hospital before his death. He presented a loud mitral systolic murmur, and the spleen was felt to be enlarged. Pyrexia was constantly present, of an irregular type—remittent, intermittent, and at times continued. The daily fluctuations were, as a rule, considerable, and at different times he had severe rigors, in which the temperature rose to 104° F., 105° F., or even higher. Some, at least, of these rigors were associated with embolism—one in particular with sudden blockage of the right brachial artery. A short time before his

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death a blood-count revealed a polynuclear leucocytosis of 29,000. No cultivations were made from the blood during life; indeed, the case was assumed to be a streptococcal one, and anti-streptococcus serum was unavailingly administered.

The following are the facts of importance revealed at the *post-mortem* examination:—There was no pericarditis, but a quantity of clear fluid was present in the pericardium. The heart weighed only 9 oz.; the left ventricle was dilated, and some fatty degeneration of the myocardium was present; there was no old endocarditis, but on the auricular surface of the mitral valve were a number of firm, rounded masses, some as large as a bean; these were pale yellow in colour and of a peculiar consistency, which was compared with that of herring's roe. The appearances were peculiar, and suggestive of something out of the common. The rest of the heart was natural except for a minute fibrinous vegetation on one aortic cusp. Large embolic plugs, with associated thrombi, were found in the right brachial and right femoral arteries, and in the latter situation there was a little commencing suppuration round the vessel. A large suppurating infarct in the spleen had caused rupture of its capsule, and set up a localised perisplenic abscess of considerable size; there was no general peritonitis. One or two smaller infarcts were present also in the spleen, and there was the scar of an old infarct in one kidney. The kidneys showed subcapsular hæmorrhages. Nothing abnormal was found in the liver, intestines, or other parts of the alimentary canal.

Cover-glass films were prepared from the mitral vegetations, and showed enormous numbers of small bacilli, some of which exhibited bipolar staining. No other organisms could be detected. Films from the spleen showed the same organism in similar numbers. With them were here associated a few larger bacilli, presumably anaërobes, as they did not grow on ordinary surface cultures. Sections of the vegetations were prepared, and one is exhibited under the microscope. It is a frozen section, stained in methylene blue; paraffin sections could not be prepared, as the mass became of stony hardness and brittleness in the process of embedding. The section shows a very singular condition. Clumps and patches of the bacilli are present here and there throughout the vegetation, and at the base of the valve they form plugs in the small vessels. But

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at the surface of the vegetation the bacilli are arranged in threads and chains at right angles to the free margin, forming as it were a kind of dense mycelial brushwork of very striking aspect, and quite unlike the appearance which one usually associates with *B. coli communis*. The bacillus does not stain by Gram's method.

That the organism was truly *B. coli communis*, or rather one of its numerous varieties, was shown by cultivation. Practically pure cultures were obtained both from the vegetations and from the spleen. The bacillus proved to be feebly motile, and to resemble *B. coli communis* in shape and size. On gelatin it grows like that organism, without liquefaction; perhaps it spreads over the surface less than the typical form. On potato it forms a moist brownish layer. Gas is very abundantly formed in glucose gelatin shake cultures. Neutral red is vigorously reduced in agar-agar shake cultures, and in broth. Milk is not clotted until the fourth day. Indol formation is absent, even after five days' incubation, but this character is almost the only one in which the organism departs from the classical type of *B. coli communis*, of which it is obviously only a variety.

Singularly enough the bacillus proved non-pathogenic upon animals. A guinea-pig and a mouse were inoculated subcutaneously from a forty-eight hours' broth culture, receiving a cubic centimètre and half a cubic centimètre respectively. Both animals remained unaffected, not even a local inflammation being excited, and this although the inoculations were performed within a day or two of isolating the bacillus, before it could be supposed that time had elapsed for its attenuation.

I trust that the specimens and cultures which are exhibited are sufficient to convince the Society that the case described is in truth a primary endocarditis due to infection with *B. coli communis*. The case, though a pathological rarity, is by no means unique. Similar cases have been recorded by Netter and Martha, by Gilbert and Lion, and by Hitschmann and Michel; there may be other records which I have failed to come across. The organisms described by Weichselbaum as *B. endocarditis griseus* and *B. endocarditis capsulatus* can hardly be identified with this, as the former is described as staining by Gram's method, and resembling the xerosis bacillus in appearance, while the latter is distinctly capsulated, and resembles

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Friedlander's pneumo-bacillus. The pyogenic properties of *B. coli communis* are so well established that no special interest attaches to the perisplenic abscess in the case described.

November 19th, 1901.

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5. *A case of muscular hæmorrhage in typhoid fever.*

By F. W. Andrewes.

Myositis and intra-muscular hæmorrhages are sufficiently unusual complications of typhoid fever to warrant the placing upon record of an accurately observed case which admits of an explanation of the pathological processes involved.

The patient was a carman, aged 18 years, the subject of chronic double otitis media, admitted to St. Bartholomew's Hospital during the third week of an attack of typhoid fever. It was a typical case and a severe one. Rose spots, diarrhœa, and the usual phenomena of the disease were well marked; the serum reaction was characteristic. Before the temperature became normal he had a relapse, and in this relapse he died on the fifty-second day from the commencement of his illness. During the whole time he was under observation he was extremely ill, and during the relapse, so ill that he was unable to make intelligible statements as to his symptoms; his pulse at this time was feeble, very dicrotous, and had a frequency of nearly 150.

Two days before his death it was noted that he showed signs of pain when turned on to his left side, and on the day before he died there was found considerable swelling of the left thigh. The swelling gave to the hand the sensation of deeply seated fluid, and it was judged to be a hæmorrhage. Besides the local tumour in the thigh there was œdema of the whole limb, and subcutaneous hæmorrhages were noticed about the feet and elsewhere. It was not suggested that any septicæmic infection existed apart from the typhoid fever. No secondary infection could have rendered him more ill than he already was.

The *post-mortem* examination was performed thirty-two hours

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after death by Dr. Morley Fletcher. The lesions found were those of typhoid fever, swelling and ulceration of a few of the Peyer's patches at the lower end of the ileum, with very numerous small ulcers occupying the solitary follicles of the colon. The spleen weighed 13 oz. and was soft; the liver was pale and soft, and showed a few subcapsular hæmorrhages. The blood was very fluid; endocarditis was absent, and the great vessels were natural. There was no plugging of arteries or veins in the left thigh, so far as they could be followed out in the *post-mortem* room. The swelling in the left thigh was due to a diffuse extravasation of blood into the substance of the vasti and crureus muscles, especially the vastus externus; the rectus femoris had escaped. There was no rupture of the muscular fibres. The interstitial character of the extravasation is well shown in the specimen exhibited, which is a longitudinal section of one of the muscles prepared after fixing in formalin. No other muscles in the body were found to be affected, though only those usually exposed in a *post-mortem* examination were inspected.

Portions of the affected muscle were at once submitted to microscopic examination teased up in salt solution. The muscular fibres were in part normal, or, at least, unaltered in size, and retaining their natural striation. Many of them, however, were swollen and hyaline, with loss of striation, and a tendency to split up transversely into short segments; the appearances, in fact, characteristic of the waxy or hyaline degeneration of muscle first described by Virchow, but generally associated with the name of Zenker, from his careful description of the phenomenon in typhoid fever. The teased specimen shown this evening is prepared from some of the muscle which has been preserved in glycerin, without any preliminary hardening; it still shows the degeneration of some of the muscle fibres fairly well. In addition to the changes in the muscle fibres, blood-corpuscles were, of course, abundant, and attention was also at once attracted to enormous numbers of cocci present in the preparations. A stained film of the muscle juice showed that these were streptococci in small groups and short chains. Cultivations confirmed this. From the muscle a streptococcus was obtained in practically pure culture, no typhoid bacilli being present. Dr. Gordon kindly tested the organism,

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and reports that it corresponds in all respects with the type of *Streptococcus pyogenes*. Cultures were also taken from the heart's blood and spleen; these yielded a medley of organisms (the weather was hot, and thirty-two hours had elapsed since death), but amongst these streptococci were found. It is therefore clear that the patient was suffering when he died, not only from typhoid fever, but also from a secondary septicæmic infection with *Streptococcus pyogenes*. There is also every reason for supposing the muscular lesion to be associated with the latter infection rather than directly with the typhoid infection.

Portions of the affected muscle were hardened in Müller's fluid and cut in paraffin, both longitudinally and transversely to the long axis of the fibres. The sections, some of which are shown to-night, were stained in various ways. The distribution of the streptococci is best seen in sections stained first with carmine and then by Weigert's fibrin stain. They occupy the perimysium, and are not uniformly distributed; in places, especially about the arteries and veins, they are present in enormous numbers. The hæmorrhage is well seen in all the sections; the muscle fibres are everywhere separated by distended capillaries and extravasated corpuscles, which in places occupy considerable areas of the section. The hyaline degeneration of the muscular fibres is well shown in sections stained by van Giesson's method; the affected fibres are seen to be swollen and devoid of striation; they are occasionally split into transverse segments, and they stain of a deep red tint which contrasts well with the fawn-colour of the unaltered fibres. Of leucocyte aggregation there is little or no evidence.

If one reads Trousseau, or others among the older writers, one finds such complications of typhoid fever as muscular inflammation, hæmorrhage, rupture, and abscess alluded to as if they were not rare. Yet this seems contrary to our experience at the present day. Perchance, with altered conditions and different treatment, the type of the disease has changed. But the main interest of the present case centres in the causation of the muscular hæmorrhage. It was apparently no part of the typhoid proper, but an accidental complication, comparable in every way, though on a larger scale, with the hæmorrhages often seen, in streptococcus septicæmia, in the skin, retina, or serous

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membranes. Its unusual seat, in a voluntary muscle, must have depended upon some chance metastasis. Whether or not the lesion is to be regarded as a myositis is open to discussion. Leucocyte aggregation in the affected area is absent or inconspicuous, but the case was an early and acute one. The initial phenomena of inflammation are there, and it is difficult to believe that an acute inflammation would not have ensued had the patient lived.

The relation of the hyaline degeneration of the muscular fibres to the lesion is also a matter worthy of discussion. Zenker, Trousseau, and others seem to have regarded these cases as due to muscular rupture on exertion, dependent upon a primary waxy degeneration of the muscle. One can hardly refuse to accept Zenker's statements as to the widespread diffusion of the degenerative changes which he met with in typhoid fever, apart from any association with muscular hæmorrhage. In more recent times, however, it has been held by J. Arnold, Weihl, and others, that waxy or hyaline degeneration of striped muscle fibres is more often a sequel than a cause of their rupture, and it is asserted that such changes may be found associated with most gross muscular lesions. This seems the most reasonable view to take in the present case, but it is to be regretted that other muscles were not examined to determine whether or not the degenerative change was present apart from the hæmorrhage. It would need a series of cases to show that muscular hæmorrhages in typhoid fever are always, or often, septicæmic in origin. Here, at all events, is one case in which that explanation holds good, and in which there is no need to assume that the degenerative changes in the muscle fibres were of more than secondary importance.

October 15*th*, 1901.

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6. *A case of gangrene of the nose associated with the* B. pyocyaneus.

By David Nabarro.

History.—The patient, G. A—, a boy aged 3½ years, was admitted into the Evelina Hospital under the care of Mr. F. C. Abbott, on September 10th, 1901, with the following history :

On September 4th the mother noticed redness of one ala nasi ; child was very feverish, and had diarrhœa and sickness at same time.

The next day (September 5th) the inflammation had spread halfway up the nose, and on the following day it began to get "black" at the tip, but his general condition was not altered.

On September 7th it was "black" further up, and part of the tip had ulcerated away.

On the 8th the condition got worse, and on the 9th a doctor saw it and thought the bone was diseased, and advised that the child be brought to hospital.

The child's parents are both healthy ; there is one other child which is healthy, and there is no history of syphilis or of tubercle. Patient wasted from birth until he was seven months old ; he has not had measles or other acute specific disease.

On admission the general condition was bad, the child being very pale and wasted. There were no rash, hæmorrhages, or enlargement of spleen or lymphatic glands. Temperature was 101·4°. Pulse very small and feeble, 132 per minute.

Locally there was a black slough about the size of a shilling affecting the septum nasi, the upper part of the upper lip, and both nostrils, but chiefly the left. Considerable inflammatory swelling was present all round the slough, which was slightly separated at the lower border.

Thinking that the case might possibly be one of acute lymphatic leukæmia, a series of which was described some time ago by Drs. Rose Bradford and Batty Shaw, in which gangrenous stomatitis was a marked feature, the patient's blood was examined, but there was only a slight leucocytosis and no abnormal increase of lymphocytes found. Rouleaux formation

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was normal and not absent as in cases of Raynaud's disease. As the gangrenous inflammation appeared to be increasing rapidly, Mr. Abbott decided to operate shortly after the child was admitted to hospital. Under chloroform the slough and surrounding inflammatory area were dissected away, the edges pared with scissors, and the surfaces of the wound rubbed over with chloride of zinc (40 grs. to the ounce). The child recovered well from the operation, the nose rapidly healed, and with good feeding the general condition improved. The temperature fell to between 99° and 100° F. immediately after the operation, and remained fairly normal until September 24th, a fortnight after the operation. The child then developed German measles (with a temperature of 101·4° for one day), and was sent to the Fever Hospital.

On October 30th he was readmitted to have a plastic operation performed, but considering the intensity of the inflammatory process and the amount of tissue removed by operation, it is remarkable how little deformity resulted.

The urine was normal the whole time patient was in hospital.

The examination of the tissue removed by operation may be divided into two parts: (1) macroscopic and microscopic; (2) bacteriological.

(1) The excised portion measured about 1¼ to 1½ inches in length by 1 inch in breadth, being irregularly oval in shape. The central portion consisted almost entirely of necrosed tissue with a hard, black slough on the surface, and was separated from the living tissues around by deep grooves in which was some greenish pus. A longitudinal section through the whole of the excised portion showed the necrotic part in the centre with the slough on the surface, and a part of the cartilage of the ala nasi in the interior, separated by a groove from the living tissues on either side. Sections cut in paraffin and stained by hæmatoxylin and eosin and by Ehrlich's triacid stain show that in the necrosing areas in the centre the structure of the several tissues can hardly be made out, the tissues taking the stains badly, and that the superficial epithelium is necrotic. The adjacent areas show great infiltration with round-cells, and the vessels here are dilated and filled with blood. In the section stained by the triple stain, it is seen that the epithelium ends abruptly at the groove between the slough and

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the inflamed area, and that many red blood corpuscles have exuded all along the line of demarcation.

Sections were stained by methylene blue and by Gram and eosin to show the organisms present. Those stained by the Gram-eosin method showed many organisms—probably all streptococci—occurring in pairs and short chains; a few were apparently capsulated and lancet-shaped, rather suggestive of the pneumococcus of Fraenkel. The cocci were not distributed throughout the section, but localised to the edge of the slough and to the area around the nasal cartilage, and formed also small plugs in the capillaries. The organisms, moreover, were found only in the central or necrotic part, and not in the inflamed tissues around. In the section stained by methylene blue many more organisms were seen than in the Gram section. The increase was due entirely to the presence of a large number of bacilli, some very long and slender, others shorter and thicker, scattered about in groups throughout a large part of the necrotic area.

(2) *Bacteriological examination.*—Cultivations were made on agar and incubated at 37° C. under aërobic and anaërobic conditions (in a Buchner's tube). The anaërobic culture showed signs of growth in twenty hours, but no coloration of the medium, and even after six days' incubation no green colour or fluorescence was present, and there was less growth on the medium than in the aërobic tube after one day's incubation, so that the anaërobic conditions not only inhibited the formation of pigment, but apparently retarded the growth of the organisms present. After removal from the Buchner's tube on the sixth day no trace of offensive gas was present in the culture-tube, which was subsequently allowed to grow under ordinary conditions. It began then at once to colour the medium typically of *B. pyocyaneus*. The agar inoculated from the excised tissue and grown under aërobic conditions at 37° C. showed in twenty hours a grass-green coloration at the upper part of the medium, while below discrete small colonies of growth were visible. In three days the whole of the medium was coloured, showing the typical appearance of a culture of *B. pyocyaneus*. Films stained by simple stain showed bacilli chiefly, while by Gram the bacilli were unstained and cocci (in pairs and chains) were visible (streptococci). This "original"

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agar on the second day of incubation was inoculated into broth, which, after twenty hours' growth at 37° C., showed marked turbidity and slight fluorescence; in hanging drop small, very motile organisms were seen, and in films only bacilli, which were decolourised by Gram's method. A gelatin stab was also inoculated from the original agar. After twenty hours, growth was apparent along the stab line, but no liquefaction had occurred. On the fourth day liquefaction had begun with a greenish colour in the medium; a few small gas bubbles were present in the depths of the gelatin. At the end of seven to eight weeks the gelatin was entirely liquefied, but not coloured green until the plug was removed and air allowed to enter the tube. A film of this liquefied gelatin showed the presence of bacilli and of streptococci. After standing at the room temperature for eight weeks a loopful of the liquefied gelatin was smeared over two agar tubes, and in twenty-four hours both the *B. pyocyaneus* and streptococci had grown.

The original agar culture, when three weeks old, was inoculated into broth, and after twenty-four hours' incubation at 37° C., the broth was markedly turbid and greenish in colour. Agar plates were made and colonies of *B. pyocyaneus* and of streptococcus rapidly developed. A single colony of *B. pyocyaneus* from the plate was subcultured into broth, and after having grown for eleven days at 37° C., 1 c.c. of the culture (which had a bright green colour) was inoculated into the left groin of a guinea-pig. The animal became ill very soon after the injection, and was found dead the next morning. At the autopsy there was much congestion of the left side of the abdomen and thorax, with much œdema fluid between the skin and abdominal walls. Many feebly motile organisms were seen in a hanging drop preparation of this œdema fluid, and in films stained by Loeffler's methylene blue short bacilli were present staining rather irregularly.

The spleen was not enlarged, and a few doubtful bacilli were seen in sections. The liver and kidneys appeared normal to the naked eye, but on section very marked cloudy swelling of the cells was apparent, and in the kidneys congestion of the vessels, especially in the medullary part. A few organisms were seen in the sections of liver, but none in the kidneys. The heart blood was firmly coagulated, and no organisms were seen in the

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films. The heart muscle was apparently normal, the lungs were a little congested; lymphatic glands were not enlarged.

The animal had probably died from toxæmia and not from a septicæmia, and the toxines were very virulent, seeing that within two hours of the injection the guinea-pig was very ill and died, probably, within twelve hours.

Cultivations were made from the œdema fluid on various media, and from all of them a pure culture of *B. pyocyaneus* was obtained.

Since the patient's readmission to hospital, his blood has been examined for organisms with a negative result; and a serum rèaction performed with a culture of the *Bacillus pyocyaneus* was inconclusive, because the control preparation showed agglutination of the bacilli, although this phenomenon was much less rapid and pronounced than with the patient's own serum.

Remarks.—From the clinical point of view the case is an interesting one, inasmuch as "idiopathic" gangrene of the nose, if one may so designate it, is uncommon. Mr. Abbott, under whose care the case is, and to whom I am indebted for permission to utilise the clinical records, states that he has never seen a condition exactly like that seen in this patient, and regards it as septic.

Owing to the presence of at least two organisms in the diseased area, it is difficult to decide which is the actual cause of the gangrene, but for several reasons I am inclined to think that the *B. pyocyaneus* has played an important part in the production of the gangrene. In the first place, the inoculation into the guinea-pig showed that the bacillus was possessed of a high degree of virulence, and had produced such potent poisons that the animal died in twelve hours. Secondly, the cocci are most abundant along the edge of the gangrenous area, whereas the whole of the necrosed tissue is pervaded with the bacillus. Thirdly, infection with streptococci is not at all uncommon, but a condition of rapid death of tissue such as was seen in this patient is unusual, and, we may presume, was due to an unusual cause, and infection with the *B. pyocyaneus* would be such an unusual cause. It is possible that the origin of the condition was twofold, the streptococci causing the rapid spread of the inflammatory process, whilst the rapid necrosis and

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sloughing were due to the action of the powerful toxines elaborated by the *B. pyocyaneus*.

One may add, in conclusion, that there was no evidence of thrombosis or embolism, arteritis, Raynaud's disease, or of any acute specific fever, which are amongst the more common causes of gangrene in children. *December 5th*, 1901.

7. *A case of pleuro-œsophageal fistula.*

By H. Thursfield.

In March, 1900, a boy, aged 4½ years, was admitted to the Hospital for Sick Children, Great Ormond Street, under the care of Dr. Penrose, to whom I am indebted for permission to record the case. His history was that in the previous October he had suffered from bronchitis and "congestion of the lungs," and had never completely recovered. Six weeks before admission, that is, nearly four months from the beginning of his illness, an abscess had formed on the right side of his chest. This had been incised, and a large quantity of offensive pus had escaped. On admission he was an anæmic, wasted child, with high fever, clubbing of the fingers, blue colour, and marked flattening of the upper part of the right chest. In the sixth right interspace, just below the nipple, were two ragged discharging sinuses, from which escaped offensive pus. A probe was passed into these to its full extent, and penetrated, doubtless, into the pleural cavity.

At the operation next day a piece of rib was excised in the posterior axillary line, and the empyema cavity emptied; the lung was found collapsed and bound down. The progress of the case was not satisfactory, for though the original sinuses healed without further trouble, the purulent discharge from the cavity did not diminish, and the child's general condition did not improve. Accordingly, at a further operation, pieces of two ribs were removed to secure more efficient drainage. Four days later curdled milk in small quantity was found in the dressings of the resection wound, and from this day until his death, a fortnight later, food taken by mouth was excreted from the

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wound, though never in any considerable quantity, and always liquid; solid particles were never seen. Ten days before the death of the patient two other children in the ward were isolated for pharyngeal diphtheria, and on the following day the patient's temperature reached 103·6°, and the resection wound was found greatly inflamed, with a grey sloughy membrane covering the granulating surfaces. This was twice examined for the Klebs-Loeffler bacilli, but with negative results. The patient died of exhaustion. At the *post-mortem* examination the organs, with the exception of the right pleura and lung, and the œsophagus, were found quite healthy. There was no tubercle found anywhere in the body, and there was no amyloid change in any of the organs. The right pleural cavity was a large abscess cavity with rugose reticulated walls containing flakes of lymph and pus; the ribs were quite free from disease, even in front at the seat of the original opening; the lung was shrunken into the vertebral groove, and completely carnified. Opposite the head of the third rib was a small ragged opening into the œsophagus. The opening, which is marked in the specimen shown by a glass rod, was about the size of a No. 3 red rubber catheter. On the œsophageal surface the edges were quite smooth, and there was no swelling or infiltration of the mucous membrane. From the appearances it seems probable that the ulceration had proceeded from the pleura to the œsophagus rather than *vice versâ*. There was no evidence of the presence of any foreign body.

The case illustrates well one of the most unusual complications of a neglected empyema. I have found recorded previously two similar cases, one by Dr. Osler, the account of which I have not been able to procure, and the other by Dr. Voelcker in the Clinical Society's 'Transactions' for 1890. I am indebted to Dr. Voelcker for a reprint of his account of the case, from which it appears that the empyema was of considerably longer standing than in the present case, and the destruction of tissue much greater, ribs and vertebræ being extensively necrosed. Dr. Voelcker was unable to find any cause for the œsophageal fistula, except the empyema, and concludes, as I have ventured to do, that the opening was caused by ulceration from the pleural surface into the œsophagus. In his case the opening was on the left side. The complication is rather of pathological than clinical interest,

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for it is difficult to suggest any mode of treatment which would either prevent, palliate, or remove the lesion.

October 15th, 1901.

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8. *Aneurysm of the right Sylvian artery.*

By J. O. W. Barratt and R. M. Ralph.

The Sylvian aneurysm about to be described occurred in a female 38 years of age, who up to the last half-year of life enjoyed good health. Patient complained occasionally of dyspepsia and diarrhœa, but was never troubled with vomiting. Three months before death weakness of the left side made its appearance, speech and sight became affected, and mental failure was apparent; hearing remained good. Patient complained of "dreadful cold feelings" at the top of her head, and became deluded. When walking she required assistance, and her body was bent towards the left side.

The patient was admitted to the asylum six weeks later. According to the notes of the case, for which we are indebted to Drs. F. P. Hearder and N. Roberts, she was now suffering from melancholia, and was exceedingly suspicious. Memory of recent events was much impaired, as was also perception of time. She spoke in a half-drawiing manner, was very feeble, and showed a tendency to fall to the left side. She also complained of her sight being affected. Patient's illness terminated with asylum dysentery. A week before death patient had a right-sided seizure.

At the *post-mortem* examination there was found lying on the right island of Reil a small aneurysm of 4 mm. in diameter, situated opposite the gyri breves and arising from the main trunk of the right Sylvian artery, opposite the ascending parietal branch, the lumen of which was much narrowed at its origin. The aneurysm was of an irregular shape, being triangular in the section, and tailing off to the right where the ascending parietal artery arises. It was completely filled with altered blood-clot, except towards its outer aspect. On microscopic examination the wall of the aneurysm was seen to be

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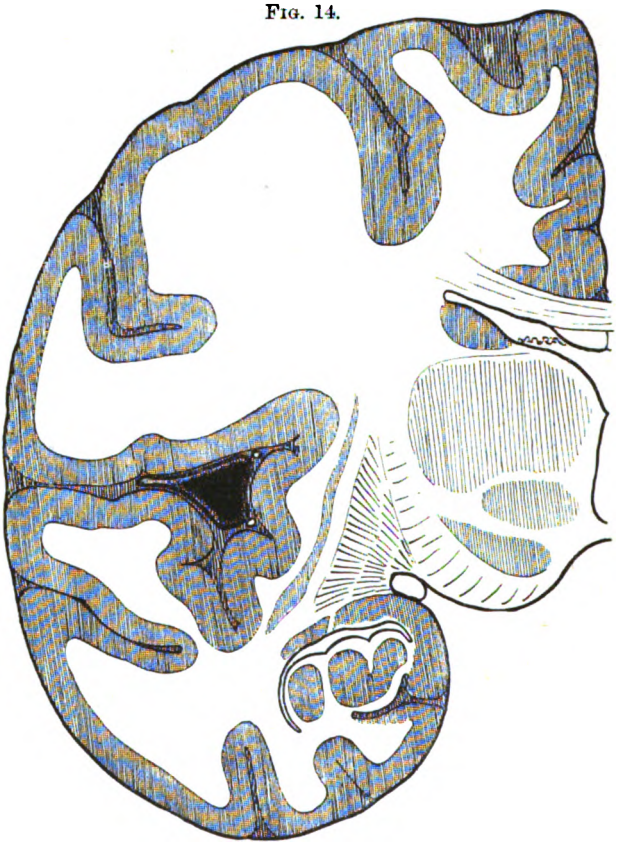
made up of connective tissue, quite free from unstriped muscle and from elastin, and containing a small number of the con-

FIG. 14.



Frontal section of the right hemisphere behind the infundibulum. The sac of the aneurysm is seen lying upon the island of Reil at the bottom of the fissure of Sylvius. Springing from the aneurysm on the right is seen the ascending parietal artery, cut across obliquely. Below and internally is seen one of the temporal branches of the Sylvian artery. Above and internally is seen another small twig which ramifies over the island of Reil. Internal to the island of Reil lie the claustrum and lenticular nucleus, beneath which is seen the right inferior cornu and pes hippocampi with the optic tract cut across. Still more internally is seen the optic thalamus separated from the lenticular nucleus by the internal capsule. The sulcus lying above the fissure of Sylvius is the lower part of the fissure of Rolando; above and towards the great longitudinal fissure is seen the ascending frontal sulcus.

centric bodies which are occasionally met with in the membranes of the brain. The contents consisted of yellowish homogeneous

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material showing little evidence of organisation. The lumen of the artery was not completely obliterated, a narrow track to one side of the sac remaining.

There was no softening or other change recognisable in the area of distribution of the right Sylvian artery. On staining by Nissl's method some defect of the stainable substance of the nerve-cell bodies in the cortex of the island of Reil and of the motor area was recognisable.

The brain was wasted, especially in the frontal and parietal regions. The pia-arachnoid membrane was opaque and thickened. The subarachnoid space and ventricles contained a large amount of clear fluid. The basal ganglia, cerebellum, pons, and medulla were free from focal lesions. The basal arteries were free from disease, with the exception of the right Sylvian.

The symptoms of left-sided paresis from which the patient suffered were obviously not caused by pressure exerted by the aneurysm, for no evidence of such pressure could be recognised on inspection or on microscopical examination, and it would indeed be difficult to understand how so small a mass lying in the fluid surrounding the wasted cerebrum could effectively compress either the convolutions of the motor area or the internal capsule, which lay at some distance from the arterial sac. The manner in which the aneurysm produced symptoms was apparently by obstruction of the blood-supply. The vessel was not, however, completely obliterated, its lumen was merely narrowed at the aneurysm, so that no softening occurred in its area of distribution though paresis of the opposite side of the body resulted. The defect of vision and difficulty of speech which were noted were presumably also due to this disturbance of circulation in the area of the Sylvian artery, and were not apparently related to the condition of brain atrophy with excess of fluid in the subarachnoid and ventricular spaces and opacity and thickening of the pia-arachnoid which were found at the autopsy, and which were obviously of longer duration than the history given by the friends would suggest. The single epileptiform seizure, which occurred a week before death, it will be noted, affected the right side.

The cause of the aneurysm is obscure. The arteries at the base of the brain were quite healthy in appearance. The valves of the heart were normal. There was commencing atheroma of

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the coronary arteries and the root of the aorta. No source of a septic embolus could be suggested, and sections of the aneurysm were free from micro-organisms. The kidneys showed chronic interstitial nephritis. No lesions were observed suggesting syphilis, nor was there anything in the history of the patient's pregnancies which suggested that affection; patient had two children living, described as healthy, and two children (twins) who died. *October 15th*, 1901.

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9. *On the general characteristics and pathogenic action of the genus* Streptothrix.

By Alexander G. R. Foulerton and C. Price Jones,

From the Bacteriological Department of the Middlesex Hospital.

[With Plate IV.]

The increased amount of attention which has been given during the last three or four years to the exact identification of the causative parasite in different cases of actinomycosis, and to the pathology of streptothrix infections generally, has led to a broadening of our conception of the term actinomycosis.

Formerly, actinomycosis, whether occurring in man or lower animals, was regarded as a single disease caused by the one parasite first described by Harz and Bollinger as *Actinomyces bovis*. But the term is now to be used as comprehending a variety of infections caused by different species of a large genus of mould fungi, the *Streptotrichea*.

And with this enlargement of the term in its strictly pathological sense, its significance in clinical medicine has necessarily extended, so that the term "actinomycosis" can now be used only as a general designation for a class of diseases, each of which is caused by a distinct specific parasite. In the present communication we propose to consider shortly the morphology and general characteristics of the genus *Streptothrix*, and to refer very briefly to the pathogenic action of different species on man.

Our observations on the general characteristics of these fungi

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are founded on the examination of such species, twenty-five in all, as we have been able to obtain from different sources. Cultures of each of these species are shown this evening.

These twenty-five species include five of those described by Berestnew, who had supplied them to Dr. Kral, of Prague, from whom we obtained them. The cultures of *Streptothrix Nocardii* are from a strain which Professsor Nocard himself was so good as to send us. Three species of *St. alpha*, *St. beta*, and *St. melanotica* have already been described by C. Price Jones in a preliminary communication (31) to this Society last year; *St. hominis* (Foulerton) has also been already described elsewhere (16). Four new species are shown, *St. luteola* (Foulerton), *St. leucea* (Foulerton), *St. leucea saprophytica* (Foulerton), and *St. erythrea* (Foulerton).

Of these four new species one, *St. luteola*, is pathogenic, and was isolated from the pus of a case of acute conjunctivitis with sloughing of the cornea. This organism can be clearly differentiated from *St. aurea*, also described as a cause of conjunctivitis by Du Bois Saint-Sévrin.

The three other species were isolated under conditions which suggest that they are saprophytic in their nature. *St. erythrea* was obtained by Dr. Slater, of St. George's Hospital, who very kindly handed it over to one of us for examination, as an accidental contamination on some culture tubes of horse serum which were in process of sterilisation. *St. leucea* and *St. leucea saprophytica* have been isolated from samples of sewage and from a drinking-water supply respectively, the former organism appearing to have a fairly wide distribution. Both these last two species show general characters common to several of the purely saprophytic species of the genus,—that is to say, they both liquefy gelatin, and exercise a diastatic action on starch; both have a pronounced mouldy smell, and when growing on solid media show a free formation of aërial hyphæ, which causes cultures to become more or less covered by a white chalky efflorescence. The two species have, however, certain characters which enable one to distinguish them from previously described organisms.

The remaining eleven species which we show this evening are from cultures which we have obtained from various laboratories. Each species has cultural characteristics which enable its

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separate identity to be established, and in every case the original description of the organism has been referred to, and such description compared with our own observations.

Nomenclature.

Some confusion has arisen from the fact that various writers have adopted different systems of nomenclature for this genus. Thus *Actinomyces, Cladothrix, Oospora, Nocardia,* and *Streptothrix* have all been used as synonymous generic terms. At the present time three of these terms have gone out of common use, and we are left with only two, *Actinomyces* and *Streptothrix,* to choose between. There is something to be said both for and against the use of either of these terms; the question is really only one of convenience, but unfortunately there seems little chance of pathologists coming to a common agreement as to which of the two should be retained. For ourselves, we prefer to use the term *Streptothrix,* and in this we are in accordance with Rossi-Doria, and the majority of British and American pathologists. Others, however, prefer to retain the older term *Actinomyces,* and amongst these are Gasparini, Berestnew, and Lachner-Sandeval.

With regard to the nomenclature of the species mentioned in the appendix to this paper, there are one or two points which need explanation. The so-called *Cladothrix dichotoma,* which has been a fertile source of confusion in the history of the classification of these species, is described under the name *Streptothrix nigrescens.* The culture which we thus describe appears to correspond with *Cladothrix dichotoma* of the majority of writers. Other writers have identified *Cladothrix dichotoma* of Cohn with *Streptothrix nigra* of Rossi-Doria and *Actinomyces* (*Streptothrix*) *chromogenes* of Gasparini. The culture which we describe as *Streptothrix nigrescens* can be distinctly differentiated from *St. nigra,* and from an organism which we obtained from Kral as *St. chromogenes.* The last organism presents some slight variations in character when compared with *St. nigra,* with which many take it to be identical.

Another alteration in current nomenclature which we have made is in describing *Actinomyces* (*Streptothrix*) *bovis* of Harz

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and Bollinger under the name of *Streptothrix bovis communis*, an alteration which seems to be advisable since other species have been described as infecting the ox. *Streptothrix alba* is possibly the same organism as that originally described by Cohn under the name of *Streptothrix Foersteri;* but this is a question which cannot be decided with any certainty. *Streptothrix odorifera* of Rullmann was originally isolated from soil (34), and subsequently this writer described under the same name another organism which had been isolated from the sputum of a case of lung disease (35). The descriptions of the organisms derived from these two sources do not seem to correspond accurately, and the species which is described in our catalogue under this name appears to be the saprophytic species isolated from the soil; the culture on which our description is founded was obtained from Kral, and, as we understand, came originally from Rullmann himself.

Morphology and development.

Among the best of the earlier descriptions of the morphology of the species then known as *Actinomyces bovis* we may particularly mention that of Professor John McFadyean (26), who, in 1889, published a very full account of the fungus as it appears in the ox, and that of Domec (10), who gave a detailed description of its morphology in cultures on artificial media, together with an accurate account of the spore formation, and also described the sprouting of new mycelium from the spores. Domec also went very fully into the reasons for regarding these spores as being really the spores of a mould fungus, and insisted on the fact they did not represent either a vegetative or spore form of a fission fungus. Since these two papers, many contributions to our knowledge of the characteristics of the species of this genus have been made by Rossi-Doria (33), Gasparini (19), Sauvageau and Radais (37), and more recently by Levy (24), Hayo-Bruns (8), Berestnew (5), and Lachner-Sandeval (23), to mention only some of the number of those who have worked at or written about the subject.

The following description of the general morphology of the genus is founded on our observation of the development and

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growth of the twenty-five species which we have cultivated and studied under different conditions.

A streptothrix in the mature form, seen in comparatively young cultures on artificial media, appears as a tangled mass of branching mycelium, the chief, or parent, threads of which may be straight, or may show a more or less wavy, or a distinctly spiral outline. The branching of the chief threads results from a lateral budding out, and there is no appearance of what is termed "false branching." Branching by dichotomy, that is to say, by the terminal division of a filament into two others of equal size, has been described by some writers, but we have failed to satisfy ourselves that this method of division occurs in any of the species which we have examined. The lateral branches are set at varying intervals along the parent threads, and different species may present much variation in the frequency with which lateral branching occurs; differences in this respect may be seen also in cultures on different media even with the same species. These lateral branches not infrequently show a distinct constriction at their base where they spring from the parent thread. They also present considerable differences in the structure of their terminal part; not merely is this so in different species, but variation may be observed in the same species under different conditions of culture. Thus the extremities may taper regularly to a point, or may be lance-shaped, or may present a cylindrically thickened or globular termination. When the fungus is growing on the surface of a medium, the lateral branches may rise erect from the general mass of mycelium as microscopic aërial hyphæ. When these aërial hyphæ undergo the process of chain sporulation an appearance as of an efflorescence results in many species.

The next stage in development is characterised by the occurrence of an alteration, which has the appearance of a degeneration, of shorter or longer segments situated at intervals irregularly along the course of the mycelium. These altered lengths of mycelium no longer retain the stain when treated by Gram's method, and stain but faintly with the ordinary basic aniline dyes; they present the appearance of a faintly stained cylindrical sheath which has lost its former contents and has collapsed.

In coincidence with this change in the mycelium, the first obvious evidence of sporulation is usually seen. In many of

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the filaments and lateral branches the terminal portion assumes a regularly beaded appearance, produced by a transverse segmentation which affects the whole substance of the mycelium. When stained the extremities now present a regularly beaded appearance; the portions of mycelium which represent spores staining deeply with aniline dyes and retaining the stain when treated by Gram's method, whilst the regularly intervening portions no longer hold any stain, or hold it but faintly.

This, then, is the stage of what may be termed chain sporulation, and those segments of the beaded thread which retain the stain become ultimately, with the disappearance of the intervening degenerated portions of mycelium, the free spherical spores which have been erroneously described as coccal forms of a pleomorphic fission fungus. In a microscopic preparation the free spores may appear either as more or less scattered spherical bodies, or may still retain their former chain-like arrangement.

After the degeneration and segmentation of the mass of mycelium, a process of fragmentation occurs. Those portions of the mycelium which have been spoken of as degenerated gradually disappear, and the culture now consists of free spores and isolated longer or shorter lengths of mycelium. These longer or shorter lengths of mycelium may be either of a regular, even, rod shape, or portions may retain the original wavy or spiral outline of the threads which is seen in an earlier stage in some species; they may also show short remaining portions of former lateral branches still attached. And in still older cultures nothing but spherical spores may be seen. The longer or shorter cylindrical segments formed in the fragmentation of the mycelium probably represent, like the spherical spores, more resistent forms, and at a certain stage in cultures of some species these cylindrical segments themselves show a process of chain sporulation. But so far as we have observed, chain sporulation previous to fragmentation of the mycelium occurs only at the extremity of the filaments, and never in the course of their length.

The life cycle of the fungus is now complete, and if the spores are transferred to a fresh medium, a mycelium again develops from them by a process of sprouting. It is probable that a new mycelium may also sprout from any short cylindrical seg-

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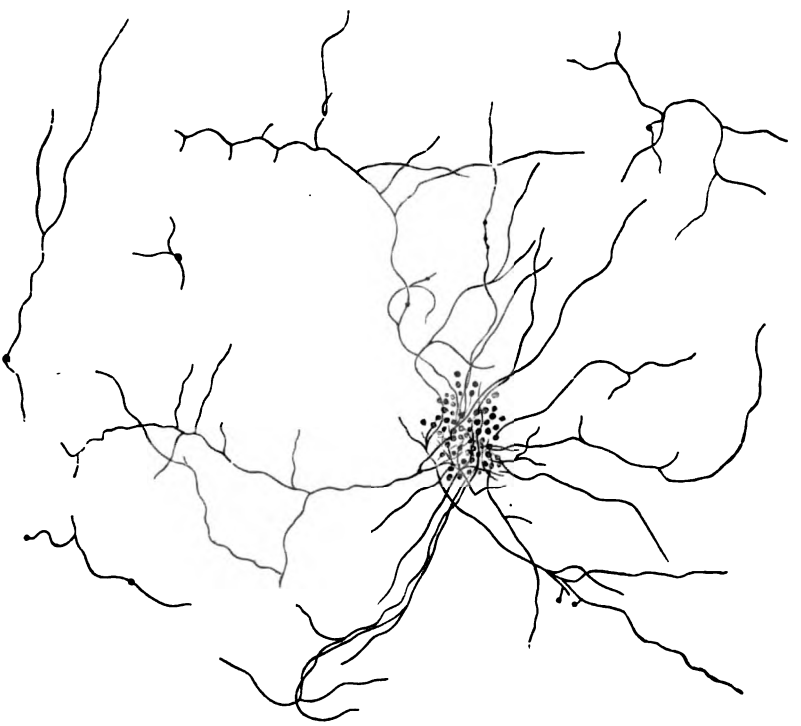
ments of the former mycelium that may have persisted side by side with the spores. Under no conditions have we ever seen anything which would suggest that these short cylindrical segments can give rise to similar short segments without an intervening development of a regular mycelium; nor has the least indication of any multiplication by fission been seen either in

FIG. 15.



Hanging drop sub-culture in broth of streptothrix from pure spore culture, twenty-four hours on warm stage. Drawn under Zeiss one-twelfth oil immersion, eye-piece No. 4, by Mr. C. Price Jones.

them or in the free spores. The only change which occurs in the free spores is the development of mycelium by a process of sprouting, which may readily be observed by incubating the spores of one of the more quickly growing species in a hanging drop culture at a temperature of 37° C. At the end of eighteen or twenty-four hours it will be seen that the spores have given

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rise to a number of mycelial threads, one, two, or three such sprouting out from each spore, and at the end of this time the mycelium will already show later branches in some cases.

In connection with the question of development, we would emphasise the fact that the formation of short lengths of mycelium by a degeneration of intervening portions of the thread is a process which differs essentially from that of clean fission, without obvious loss of substance, by means of which reproduction occurs amongst the schizomycetes. In certain of the more slowly growing pathogenic streptotricheæ the regular cycle of development may be difficult to follow in cultivation on artificial media, growth being slow, and fragmentation of the mycelium occurring almost coincidently with growth. Therefore at whatever stage a growing culture of such a species is examined, there will always be a relatively large proportion of mycelium which has already undergone fragmentation. If, however, preparations from cultures on artificial media are carefully examined at different stages of growth, and if the appearances presented by the organism when thus growing are compared with the forms which occur when the parasite is growing under natural conditions in a living host, distinct evidence of the occurrence of the usual cycle of changes will be found.

The following measurements of various streptotricheæ at different stages of development were made from stained and fixed specimens; they must therefore be taken as only approximately correct. In a twenty-four hours old culture of *St. Nocardii* the transverse diameter of the unbroken mycelium was ·65 μ; in an older culture in which fragmentation had taken place, the short portions, which still retained the Gram's stain, measured 1 μ and upwards in length, and ·6 μ in transverse diameter; in a six weeks old culture the diameter of the spherical spores was ·6 μ. In the case of *St. caprae* the transverse diameter of the mycelial threads in a twenty-four hours old culture was ·7 μ; the diameter of the spherical spores in a six weeks old culture was ·65 μ. With *St. lutrola* the spores have frequently a diameter greater than the transverse diameter of the mycelium. In a three weeks old culture of the organism in broth the parent threads had a transverse diameter of about 1 μ, and the lateral branches, which in this species are some-

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what constricted where they spring from the parent thread, measured from ·65 μ to ·7 μ across; the free spores seen in a six weeks old culture measured from 1 μ to 1·2 μ in diameter.

Staining characteristics.

The general staining properties of the mycelium have been referred to already. In the species which we have examined the adult threads before any change of the nature of segmentation has occurred, the shorter or longer lengths of resistent mycelium, and the free spores, all stain well by Gram's method as a general rule. But with some species, when growing on artificial media, there is sometimes a tendency to irregularity in staining by this method,—that is to say, an occasional subculture will, for no obvious reason, part with the stain after a comparatively short washing in absolute alcohol. The cause of this variation must be some departure from the normal in the chemical constitution of the mycelium, and, as a matter of fact, the great variability in pigment production in certain species would lead us to suspect that these organisms are very readily affected by slight differences in the composition of artificial media on which they are growing. This variability under the conditions of artificial culture is, of course, commonly met with in some of the higher mould fungi.

One property of especial interest in some pathogenic species is that which they share with *B. tuberculosis* and certain other organisms of staining by the Ziehl-Neelsen method. This point has been investigated in all our twenty-five species. The exact procedure followed was—first the specimen was stained in warm carbol-fuchsin for fifteen minutes, then, after washing with distilled water, it was kept in a 33 per cent. solution of nitric acid in water for two minutes; at the end of that time the cover-glass was washed in absolute alcohol for ten minutes, and then counter-stained. Tested in this way *St. Nocardii* and *St. caprae* showed a certain number of short segments, which were both acid-fast and alcohol-fast. *St. hominis*, of Sabrazès and Rivière, and *St. Eppingeri* showed a certain number of segments which were acid-fast but not alcohol-fast, the carbol-fuchsin stain surviving the washing in acid, but being discharged in the absolute alcohol. In the case of these four species, at first

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apparently no portion of the unfragmented mycelium is acid-fast; as the culture grows older a number of lengths of mycelium acquire the property of holding the stain after treatment with acid. The proportion of acid-fast segments present increases up to a certain point with the age of the culture, but even in cultures more than eight weeks old the actual number of acid-fast elements to be seen in a field of the microscope was never very great. It is further to be noted that apparently it is only the lengths of mycelium which persist after fragmentation that acquire this property; we never found free spores acid-fast. We were not able to demonstrate this staining property in any of the other twenty-one species. This negative result must, however, be accepted with reserve; it is obvious that when it occurs this acid-fast property is acquired by cultures at different ages, and as this point was, in the case of some of the species in which we failed to find any acid-fast portions, tested in a small number of cultures, it is quite possible that its occurrence may have been overlooked.

Resistance to heat.

The thermal death-point has been determined approximately in the case of all the species examined except one (*see* Appendices I and II), the time of exposure being thirty minutes, and all the cultures tested being sporing ones unless the contrary is stated. It will be seen that some species will not survive an exposure of this duration at a temperature of 45° C., whilst others will survive a temperature of 70° C., but not one of 75° C. A marked difference in this respect has sometimes been found useful in assisting to differentiate somewhat similar species (*see* Appendix I). The different heat resistance of pure mycelial and of spore-containing cultures is a matter of practical importance, in view of the fact that it has been denied that the spherical bodies seen in old cultures are true spores. Domec (10) tested the heat resistance of the unsegmented threads and of the spores in the case of *Actinomyces bovis* of Harz, and found that whereas the unbroken threads were killed by an exposure of five minutes' duration to a temperature of 60° C., the spores would survive such an exposure, but were destroyed by exposure at 75° C. for the same length of time. Vincent (43), again, has noted in the case

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of *St. maduræ* a distinct difference in the heat resistance of sporing cultures and cultures free from spores. When investigating this point we found that with some species there was great difficulty in making sure that sporulation had not already commenced in cultures which we wished to test as being free from spores. We were, however, able to get satisfactory results in the case of, at any rate, five species. Thus with *St. alpha*, *St. beta*, and *St. melanotica* we found that the thermal death-point was between five and ten degrees higher in the case of spore-containing cultures than in the case of cultures free from spores. In the case of *St. luteola* the following results were obtained :—Sporing cultures survived an exposure at 75° C. for twenty minutes, but were killed by exposure to the same temperature for thirty minutes; cultures free from spores survived an exposure at 60° C. for twenty minutes, but were killed by an exposure at 70° C. for the same length of time. With *St. leucea* the death-point for sporing cultures was the same as with *St. luteola*, but with the former species cultures apparently free from spores survived exposure at 70° C. for twenty minutes, and were killed by exposure at 75° C. for the same length of time. In the case of *St. leucea saprophytica*, and also with some other saprophytic species, sporing cultures were killed at as low a temperature as 45° C., the time of exposure being thirty minutes.

Cladothrix invulnerabilis of Acosta and Grande Rossi (1), which is apparently an organism belonging to this genus, is said to survive exposure to a temperature of 120° C.

Cultural characteristics.

In their cultural characteristics the streptotricheæ show much variety; not merely do different species present strongly marked differences as between themselves, but many individual species vary very widely from time to time in the appearance which they present when growing on similar media. With only one of the twenty-five species which we have examined was there any difficulty in obtaining growth on ordinary artificial media. In the case of this one species, *St. hominis* (Foulerton), not only was there great difficulty in isolating the fungus from the patient in whom it occurred, but having once isolated it on artificial media it was not found possible to carry subcultures beyond the third generation, and in many other cases of streptothrix

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infection in man the same difficulty has occurred in the attempt to transplant the parasite from its host to an artificial medium.

The majority of our species, including saprophytic organisms, grew better at a temperature of 37° C. than at one of 22° C.; but in some of the saprophytic species pigment production seemed to be favoured at the lower temperature. One species, *St. leucea saprophytica*, does not grow at all at the higher temperature, and sporing cultures are destroyed by being kept in the incubator at 37° C. for six days; in both these respects the species differs from any other examined.

Kedzior (21) has isolated a thermophilic "cladothrix" from sewage and from river water; this organism, which appears to be a streptothrix, grows freely at a temperature of 60° C.

Growth in nearly every species which we have examined occurs more freely under aërobic than under anaërobic conditions; *St. Israeli* of Kruse appears, however, to be a facultative anaërobic organism. We may take this opportunity of correcting a misstatement which we recently made in saying, contrary to what Nocard himself had said, that *St. Nocardii* will grow under anaërobic conditions. We have since ascertained that Nocard's statement as to this organism being a strict aërobe is absolutely correct, and that we were misled by an error of observation.

Pigment production may be manifested in one or both of two ways: either the growth itself may be coloured, or the medium on which the organism is growing may become pigmented, whilst the growth itself remains of a whitish appearance. As happens sometimes with higher mould fungi, pigment production is very uncertain with some of these species, and appears to vary with small and unappreciable differences in the media on which the organism is growing; and for this reason pigment production on artificial media is in many cases of but little assistance in differentiating species.

A peculiarity which occurs with many of the species is the appearance on the surface of sporing cultures of small drops of an oily, or gum-like, transparent fluid of a pale yellow colour. We have not examined this fluid chemically, but in appearance it resembles that which is sometimes seen on cultures of other mould fungi. An "earthy" or "mouldy" smell is a constant characteristic of some species, more especially those of a saprophytic nature.

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With regard to growth on different media, we have found that, on the whole, maltose-peptone agar is the best of the solid media which we have used. And this is, we think, the best solid medium to use when endeavouring to isolate these organisms from pus or other morbid material; some have, however, specially recommended glycerine-peptone agar for the purpose.

Growth on gelatine presents little that calls for remark. In stab cultures the species which we have examined form series of superimposed colonies, more or less discoid in shape, along the track of the inoculating wire, the colonies diminishing in circumference from the surface downwards. Two kinds of liquefaction may occur: in one case the gelatine is rapidly peptonised and a freely mobile fluid results; in the other case the process seems to be rather a gradual softening of the medium, which becomes thickly viscid.

Inspissated horse-serum is not a favourable medium for any of the species examined, growth being always distinctly less on this medium than on peptone agar, with or without maltose.

Potato is a rather uncertain medium for many of these species; some saprophytic species grow well on this medium and erode its substance considerably, an effect which may be due to their diastatic action on starch. Other species refuse to grow at all on potato; and with others, again, growth is most uncertain, the inoculation of perhaps six or eight potato tubes giving only one or two successful subcultures. On potato sporulation is, as a rule, in evidence comparatively early; and it is especially on potato that the clear yellowish exudation already mentioned is to be seen.

Growth in peptone broth is usually fairly active; the mycelium forms compact, usually discoid, but in some species globular or filmy colonies, which may remain quite isolated or may cohere together in larger or smaller masses. The colonies usually collect at the bottom of the tube, or, cohering at the surface of the fluid, may form a complete veil. In some species again there is a marked tendency for isolated colonies to adhere to the side of the tube below the surface of the broth. The broth itself always remains absolutely clear; it may become darkened in appearance, or may assume a definite colour tint. Fragmentation of the mycelium and sporulation are, as a rule, of later

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occurrence in the depth of broth cultures than when the fungus is growing on the surface of a solid medium.

Growth in milk occurs with twenty-four out of the twenty-five species which we examined. Only one of these twenty-four, *St. alpha*, produces a definite and complete coagulation of the milk. In the majority a slight acidification of the milk takes place, but not in a degree sufficient to produce coagulation of the casein. In many species this preliminary acidification is followed by a peculiar change in the milk, which slowly clears from above downward, the lower part of the tube containing a very finely divided sediment. This change has been described as being produced by a peptonisation of the milk, an explanation which does not appear to us to be an altogether satisfactory one. The process appears rather to resemble a saponification, and Sabrazès and Rivière state definitely that the streptothrix which they have described is able to saponify fatty bodies and assimilates glycerine.

One important property which is often of assistance in differentiating the saprophytic species is the diastatic action on starch which some of them exhibit. None of the ten pathogenic species which we have examined possess this property.

Position of the genus in botanical classification.

The first recognised species of this genus, *Actinomyces bovis* (*Streptothrix bovis communis*), was placed by Harz amongst the hyphomycetes, and there can be no doubt that, according to our present system of classification, that position is the correct one. Many later writers, however, have disputed this arrangement, and have attempted to place the streptotricheæ amongst the schizomycetes. Such writers have seen in the unbroken mycelium, the fragmented mycelium, and the free spores respectively, the leptotrichial, bacillary, and coccal forms of a highly pleomorphic fission fungus. In other words, differences in morphology seen at different stages of growth have, for want of tracing the complete cycle of development, been taken to represent more or less permanent types. Others again, whilst recognising the spores as such, have still regarded the organism as belonging to the fission fungi. In reply to this Domec pointed out, (1) that such spores are stained by aqueous

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solutions of basic aniline dyes and by Gram's method, but cannot be stained by Moeller's method for staining ordinary bacillary spores; (2) that the heat resistance of such spores is but little greater than that of the adult form, again a point of distinction from bacillary spores; and (3) that these spores are formed by a complete transverse segmentation of the thread as with some recognised hyphomycetes, and not by an endogenous differentiation of the cell substance, as occurs with the schizomycetes.

Habitat of the streptotricheæ, and sources of infection for man.

Saprophytic species of the streptotricheæ appear to have a wide distribution in air, and are also found in water. *Streptothrix odorifera* of Rullmann (34) is a common earth organism, and similar species are of frequent occurrence in cultivated soil. The investigations of Berestnew and others have shown that several species attach themselves especially to the stems of grasses. The organism described by Mazé (26) as one of those which exist in symbiosis with certain Leguminosæ in nodules on their roots is apparently, from the account given of it, also a streptothrix.

None of the species thus occurring have, so far as we are aware, been absolutely identified with species recognised as pathogenic for man or lower animals.

A species, *St. lacertæ*, has been described by Terni (42) as infesting two lizards, *L. agilis* and *L. viridis*; and it has been suggested that these reptiles may be a means of distributing the parasites over herbage. Amongst animals lower than man, infection by streptotricheæ occurs exclusively amongst herbivorous species, so far as our present information extends; the organism *Cladothrix canis* described by Rabe (32) as occurring in dogs probably not belonging to this genus. The herbivorous species in which these infections are known to occur are the ox, the pig, the horse, the sheep, the goat (40), and the llama. Schmorl (41) has described an organism, *St. cuniculi*, which caused an outbreak of disease amongst some laboratory animals; but in this case again there seems to be some doubt as to the exact nature of the parasite.

In drawing any conclusions from the apparent special incidence of these infections in herbivorous animals, it must not be for-

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gotten that the ox, pig, horse, and sheep are animals in which the frequent occurrence of any disease is more especially likely to be noticed, whereas opportunities for identifying diseases in carnivorous animals are comparatively rare. Taking all the facts into consideration it is, however, extremely likely that the feeding habits of herbivorous animals have some bearing on their liability to streptothrix infections. Thus the upper surface of the tongue in the ox is a common site of infection by *St. bovis communis*, and there is reason to believe that the probably equally common infection of the mandible in the same animal may occur from the lodgment of the parasite with vegetable *débris* in the cavity of a carious tooth. Johne's observations on the pig are also well known; in a number of cases in which an awn of barley was found impacted in the crypts of the tonsil Johne found some species of "ray fungus" on the grain. In another streptothrix infection of cattle, the "farcin des bœufs" occurring in Guadaloupe, the infection appears to arise usually from some cutaneous lesion, and does not seem to have any immediate connection with the food as such.

With regard to streptothrix infections in man, we know that some species, which have not been satisfactorily identified, occur in the normal mouth from time to time, and it is not unlikely that the organisms found occasionally in lachrymal concretions and alveolar abscesses are amongst those thus occurring. The most common sites of primary infection in man appear to be the mandible, when the organism probably obtains access by a carious tooth, and the lung, in which case we may assume that the infection was air-borne. In other cases the primary manifestation of the disease may be an enlargement of the glands of the neck, when the obvious probable path of infection is by the tonsil. In the "Madura foot" disease, which is especially common amongst the unshod natives in parts of the East Indies, infection almost certainly takes place through some cutaneous lesion.

Soltmann has recorded an interesting case in a boy, in which the infection was probably conveyed by an awn of barley. The patient swallowed an awn of wall barley, and subsequently a large empyema of the chest developed. In the pus of the empyema an awn of barley was found, and the case proved to be actinomycosis.

The question of infection of man from cattle is at present

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undecided. In the first place, we do not know in what proportion of cases in man an actinomycosis is due to infection by the common streptothrix of cattle, *St. bovis communis*. But the evidence afforded by the cases of actinomycosis which have been fully worked out during the last two or three years would at any rate suggest that the common streptothrix of cattle in this country is not the species which most commonly infects man. The total number of cases of actinomycosis in man in which the species of the infecting parasite has been definitely ascertained is, however, as yet too small to allow of anything more than a provisional conclusion. The limited statistics which bear on this question would also seem to show that cases of actinomycosis in man do not occur more commonly in those who are specially associated with cattle than in those who are not exposed to this possible source of infection.

Meat taken as food is another possible source of infection for man that must be considered. It is probable that the ordinary temperature reached in the interior of meat during cooking is not sufficient to kill sporulating *St. bovis communis*. Thus the interior of a cooked joint does not usually become heated to much above 65° C., and in our experiments a temperature of between 60° C. and 70° C. applied for thirty minutes was required to destroy cultures; Bérard and Nicholas (6) found that for the same purpose, with an exposure of fifteen minutes, a temperature of between 75° C. and 80° C. was necessary; but on the other hand, the parts affected by actinomycosis in cattle are not, with the exception of the tongue, likely to be used for human food; and, further, our experience of the morbid anatomy of actinomycosis shows that primary infection by way of the digestive tract is most uncommon in man, unless, indeed, we accept lesions of the liver as evidence of infection from the intestine, a matter as to which there is some doubt.

Pathogenic action and species infecting man.

We can now refer only very briefly and in general terms to the pathogenic action of the species of this genus of parasites.

In the majority of recorded cases the obvious initial lesion has occurred at what was probably the point at which the

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parasite entered the body. But in other cases one finds lesions in internal parts when no indication of the site of original infection is apparent; the commonest example of which state of things is when the liver is found to be the single obvious site of infection. In explanation of this it is to be remembered that many of these species do not exercise any high degree of local virulence on the tissues infected, and that it is certain that lesions due to infection by these parasites may undergo a spontaneous and complete cure.

In the majority of cases there is not much tendency to a widespread distribution of the lesions, the infection usually extending gradually by continuity or contiguity of tissue. Thus the actinomycosis may spread gradually from the lung across the pleural sac, then through an intercostal space to the subcutaneous tissue of the chest wall, and then along and under the skin. In a minority of the cases occurring in man there is considerable dissemination of the infection throughout the body, as in the case of Sabrazès and Rivière, and in others that we shall quote.

In the disease known as "farcin des bœufs," the cause of which was discovered by Nocard (28), we have an example of an actinomycosis which may take the form of a slowly progressive, and ultimately very extensive, infection spreading along the lymphatic system.

With regard to the nature of the lesions which occur in actinomycoses, the usual manifestation of infection is the development of granulomata, which may in different cases produce all the various anatomical appearances of the lesions with which we are familiar in a tuberculosis caused by *Bacillus tuberculosis* of Koch. Histologically, there may be found amongst the tissue elements of the granuloma a few multinuclear giant-cells, and areas in which necrotic changes are in progress may also be seen.

The local action of these parasites on the tissues infected is not, as a rule, marked by an active virulence. The granulomatous nodules may break down, and pus may result, but in the case of a pure infection suppuration does not extend to neighbouring tissues; the abscess is limited to the area of the particular nodule, is discharged from the neighbouring surface, and not infrequently heals up. In connection with this forma-

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tion of pus, we have already pointed out that some of the pathogenic species manifest distinct peptonising power when growing on artificial media, although this property is usually less active in them than in many of the saprophytic species.

Clinical evidence would also suggest that these parasites do not, as a rule, produce toxins which have any markedly injurious effect on the system as a whole. In our experience it is only in long-standing cases of lung actinomycosis, or when the lesions are unusually extensive, that any marked wasting of the tissues generally is seen. And in cases in which wasting is prominently present there is usually the effect of secondary infection of the original lesions by actively pyogenic bacteria to be taken into account.

We will now refer briefly to the species of streptotricheæ which have been described as infecting man, mentioning first those whose characteristics have been fully described and can be readily recognised.

There can be no doubt but that the streptothrix described as occurring in man by Affanassiew (2) and others is the common species which infects cattle, *St. bovis communis*. But, as we have already said, it is probable that only a comparatively small proportion of the cases of actinomycosis in man are due to this cause.

St. maduræ, first fully described by Vincent (43) as a cause of mycetoma or "Mâdura foot," is a well-differentiated species. There is, however, at present, room for some doubt as to whether "Madura foot" is the result of only one kind of infection. It seems quite clear that Vincent's streptothrix is the cause of those cases of the disease in which the parasite appears in the discharge as pink or ochroid granules; but Homer Wright (45) has isolated a more highly organised hyphomyces from one of those cases known also under the name of "Madura foot" in which a parasite is found in the discharge in the form of small black granules, the melanoid variety. Another species with well-defined cultural characters is *St. Eppingeri* (13), which was isolated from a patient aged fifty-two, a glass-polisher, who came under treatment for what was diagnosed during life as cerebro-spinal meningitis. The patient died twelve days later, and after death there was found an abscess in the right cerebral hemisphere, which had discharged into the lateral ventricle. Amongst the

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other morbid changes found were a calcareous degeneration of the bronchial and supra-clavicular glands, old caseous nodules at the apices of the lungs, and what was termed a "*pseudo*-tuberculosis" of the lungs and pleura. The streptothrix was isolated from the cerebral abscess. Ferré and Faguet (14) also isolated a streptothrix from an abscess in the centrum ovale of the cerebrum. We have not been able to find a satisfactory account of the cultural characters of this organism; it may, however, as the writers suggest, have been the same species as that described by Eppinger.

St. hominis of Sabrazès and Rivière (36), which was isolated from two cases, is easily differentiated from the organism described by Eppinger. In one case the streptothrix was found in the pus of a cerebral abscess and in a suppurating infarct in the kidney, in the other case it was found in the lung in a case of "pleuro-broncho-pneumonia" and in miliary abscesses in the subcutaneous tissue—in the latter in pure culture.

We have examined cultures of the two species described by Eppinger and by Sabrazès and Rivière, and both show a certain number of acid-fast segments in cultures on artificial media.

One new species which we now describe, *St. luteola*, was isolated under conditions which leave but little doubt that it was pathogenic in a case of conjunctivitis, with sloughing of the cornea. The patient was a girl aged twelve years, who came to the Ophthalmic Department of the Middlesex Hospital with the condition described. A careful examination of the discharge from the conjunctival sac for pyogenic organisms, and particularly for *Micrococcus gonorrhœæ*, was made. In microscopic preparations only the streptothrix could be found, and on all the media inoculated, including fresh human blood-serum, the organism was obtained in pure culture. Under treatment with nitrate of silver the inflammation subsided, and the streptothrix disappeared from the discharge, which became sterile. The secretion of the sac of the healthy eye was examined for the same organism with a negative result.

Du Bois Saint-Sévrin has described another species, *St. aurea*, which also was apparently the cause of an ulceration of the cornea. The patient from whom it was isolated presented, close to the right lachrymal caruncle, an ulcer covered by a *pseudo*-membranous exudation which resembled

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in appearance a diphtheritic patch, or a chancre of the conjunctiva. The membrane re-formed rapidly after removal. The ulcer was treated with perchloride of mercury, with iodine, and with iodoform without success, but it was cured by the application of citron juice. The organism isolated from this case by Du Bois Saint-Sévrin and Mercier (12) does not correspond with any other known streptothrix.

Garten (18) has described as *Cladothrix liquefaciens II* a streptothrix which he isolated from a patient aged twenty-two years, who came under treatment with a history of illness extending over about three years. The patient was a locksmith, and the symptoms complained of were severe pain in the chest and in the right lumbar region, which together had prevented the man from following his occupation. There was a swelling in the right lumbar region, extending from the iliac crest to the level of the eighth rib. This was incised, and a chocolate-coloured pus, containing numerous yellow granules, evacuated. The pus had a very unpleasant odour, and contained filaments which showed a true branching. But neither from this pus, nor from that of various subcutaneous abscesses which subsequently formed, were any cultures obtained. After a stay of two years in hospital the patient died. In the examination after death a "labyrinth of fistulous passages and abscesses" was laid open, and from the pus in these fistulæ a streptothrix was obtained (*see* Appendix III).

Garten termed his organism "*liquefaciens II*," in order to distinguish it from the one isolated by Hesse (20) from a case which presented somewhat similar clinical features. Hesse's case was that of a wheelwright, aged thirty-two years, who came under treatment for an abscess in the left inguinal region. The abscess was incised, and a fistula communicating with the gut resulted. Afterwards abscesses formed on either side of the lumbar spine, and on the right side of the dorsal spine. The pus from these abscesses contained yellow parasitic granules. The patient also had bronchitis, but there were no granules in the expectoration. The patient died after an illness lasting for a little more than twelve months. The examination after death showed that the infection commenced as an abscess which was in direct connection with the rectum by a fistulous opening. There were numerous retro-peritoneal abscesses, and a large one

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situated on the under surface of the liver. Hesse isolated from the pus of one of the dorsal abscesses a streptothrix which, he thought, belonged to a new species (*see* Appendix III).

The species described as occurring in the preceding cases can be clearly differentiated by their cultural characters; we have next to consider a number of cases of actinomycosis in which a streptothrix has been isolated, the characters of which are either so indefinite, or have been so imperfectly described, that at present it is impossible to assign each to its particular species.

First may be mentioned *St. Foersteri* of Cohn (9); this organism, as originally described, was isolated from concretions in the lachrymal canal. Macé (25) identifies this species with *St. alba* of Rossi-Doria, with *Oospora Guignardi* of Sauvageau and Radais, and probably with *St. odorifera* of Rullmann. It is probable that this species was one of the streptothrix organisms which are not infrequently found in the mouth and in the conjunctival sac under the conditions of ordinary health, but we cannot identify it absolutely with any of the species which we have ourselves examined. From the general description given of it, this organism resembles most closely *St. alba* of Rossi-Doria, which latter we have placed provisionally amongst the saprophytic species.

Rullmann, in addition to his *St. odorifera*, which was isolated from soil, has described a streptothrix which he found in the sputum of a woman with symptoms of disease in her lungs. The organism was isolated, and studied in its growth on artificial media; a number of mice, guinea-pigs, rabbits, and a horse were inoculated. Some of these animals died, and from the resultant lesions Rullmann isolated an organism which he describes as "odorifera;" but, at the same time, Rullmann does not seem to have satisfied himself as to the identity of the organism as isolated directly from the sputum with his *St. odorifera* isolated from soil.

The organism described by Kruse in Flugge's handbook 'On Micro-organisms' as *St. Israeli* is a species isolated by Wolff and Israel (44), which grows better under anaërobic than under aërobic conditions. Levy (24) considers that the streptothrix which he has isolated from five cases of actinomycosis in man corresponds with this *St. Israeli*, and also that the organism described by Aschoff (4) belongs to the same species.

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Berestnew (5) has described the organisms which he isolated from four cases of disease which was diagnosed clinically as actinomycosis.

Case 1 was that of a woman with a subperiosteal abscess of the mandible.

Case 2 was that of a much emaciated patient, aged sixteen years, who gave a history of chest trouble of about four months' duration. There were physical signs of disease in both lungs, and a painful swelling presented under the right nipple. This swelling was incised, and a thick, pappy fluid was evacuated, from which a streptothrix was isolated.

Case 3 was that of a patient aged forty-four years, who presented several sinuses between the right nipple and the sternum, surrounded by an area of inflammation. A streptothrix was found in the expectoration and in the pus discharged from the pectoral sinuses. The patient died about twelve months after the first plain symptoms of his illness had developed.

Case 4 was that of a child aged five years, who had been ill for about a month. When first seen the child presented symptoms of a pleuro-pneumonia, and some two months later an abscess presented over the third, fourth, and fifth sterno-chondral articulations on the right side. A rib was resected, and a small pus-containing cavity in the right lung opened up. The blood-stained pus in the cavity, as well as the patient's expectoration, had a peculiar aromatic smell. A number of granules, consisting of masses of an organism, were found in both pus and expectoration. The patient died with "pyæmia" five months after the declared onset of illness. In the examination after death there were found at the apex of the right lung a cavity the size of a pigeon's egg, with broncho-pneumonia and pleuritis; on the left side of the chest, broncho-pneumonia with a diffuse pleuritis, and an abscess in the lower half of the left occipital lobe of the cerebrum. The pus of the cerebral abscess had the same peculiar aromatic smell previously noticed, and also contained parasitic granules.

The organisms isolated from the first three cases presented certain differences as compared with each other, and Berestnew considered them as being true "ray fungi," those from the first two being probably of the same species (*see* Appendix III). The organism from the fourth case Berestnew does not place

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amongst the "ray fungi," but terms it *Bacillus pseudo-actinomycosis*. With regard to this last organism, we are not quite in agreement with Berestnew as to the criteria for the identification of the true "ray fungi," and we think that it is just possible that the particular organism in question was really a streptothrix, but that the complete cycle of its development was not observed.

In connection with the last case we may mention those recorded by Dor (11) and Sawtschenko (38). Dor's case was that of a patient with an abscess at the angle of the mandible, and the pus contained numerous granules which stained by Gram's method, and consisted of long, beaded filaments. The organism was one which Dor thought might be easily confounded with a bacillus, and he considers that Sawtschenko fell into this error when he described a similar organism as a bacillus, and his own case as one of "pseudo-actinomycose bacillaire." The latter author describes as a bacillary *pseudo*-actinomycosis a case which resembled actinomycosis clinically, and the pus of which contained parasitic granules which consisted of zooglœal masses of bacilli. These "bacilli," after long exposure to oxygen, formed unbranched threads. The organism was described as an anaërobe, and did not stain by Gram's method.

The nature of these cases of Dor and Sawtschenko is a little ambiguous; the former apparently considered that his own case was an actinomycosis, whilst the latter did not so consider either. In any case the term "*pseudo*-actinomycosis" is to be unreservedly condemned, and bearing in mind the varying morphological phases of the streptotricheæ it seems not at all unlikely that the cases which have been so described were really actinomycoses.

The organism shown by us to-night as *St. hominis* (Foulerton) (16) was isolated from an Italian woman, aged forty-six years, who was admitted into the Middlesex Hospital with a history of chest trouble for ten years past. The chest symptoms had increased considerably in severity during the two years immediately preceding admission. About twelve months before admission an abscess had been opened in the left axilla, in which situation a sinus persisted, along which a probe could be passed upwards and inwards for about five inches. A

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month before admission another abscess had discharged spontaneously just above the left clavicle. On admission there was painful swelling and induration of the subcutaneous tissue on the front of the left shoulder, above and below the clavicle, and extending into the axilla. The surface involved was livid in appearance, and had scattered over it a few pustules, some small ulcers with punched-out edges, and several deeper sinuses. There was deep-seated fluctuation below the left clavicle, and physical signs pointing to extensive disease within the chest. During the patient's stay in hospital a number of small abscesses on the front and back of the shoulder were either opened or discharged themselves spontaneously. The patient left the hospital after four months' treatment, the area of subcutaneous infection having meanwhile extended considerably over the front of the chest, and over the back of the shoulder as far as the level of the spine of the scapula. Large numbers of streptothrix organisms were present in the expectoration and in the pus of the subcutaneous abscesses. From the latter source the organism was obtained in pure culture, but could not be positively identified with any previously described species (*see* Appendix I).

Hayo Bruns (8) has isolated from a case which was diagnosed clinically as one of actinomycosis of the abdominal wall, an organism (*see* Appendix III) which he thought might possibly correspond with one of Berestnew's species.

Paul Krause (22) has isolated from an abscess of the mandible an organism (*see* Appendix III) which again does not quite correspond with any previously described species.

Norris and Larkin (29) have described very carefully two cases of "necrotic broncho-pneumonia," apparently caused by a streptothrix parasite.

The first case was that of a man, aged forty-five years, who came under treatment for what was diagnosed clinically as gangrene of the lung, and died about two months after the onset of symptoms. The examination after death showed lesions which were described as being due to "an acute exudative and necrotic inflammation of the bronchi and surrounding alveoli; a broncho-pneumonia associated with a productive inflammation of the framework of the lungs and organisation of the alveolar exudate—an interalveolar and intra-alveolar pneumonia."

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The second case was that of a man aged 23 years, who came under treatment with severe chest symptoms, and died about eighteen months after the commencement of his illness. In this case the lesions were those of "an acute exudative and necrotic bronchitis, with bronchiectasis, a broncho-pneumonia, composed of alveoli filled with a cellular or fibrinous exudate, which is more or less organised, and a productive inflammation and thickening of the framework of the lungs—alveolar walls, interlobular septa, and pleura." The writers found the same species of streptothrix in each case, and concluded that it was closely related to, or identical with, *St. Israeli;* the organism, however, grew equally well either with or without oxygen.

Scheele and Petruschky (39) have recorded the case of a woman aged 56 years, who, after an attack of influenza, developed an illness characterised by irregular fever, pain in the left breast, and multiple subcutaneous abscesses, the last especially in the region of joints. The patient died after about three months' illness, and at the examination after death the following lesions were found:—There was pleuro-pneumonia on the left side; the heart was dilated, and the spleen somewhat enlarged; there were severe cystitis and pyelitis. A streptothrix was found in the sputum and in the subcutaneous abscesses, and was obtained in pure culture (*see* Appendix III). The organism as it occurred in the sputum proved acid-fast when stained by Gabbet's method.

Aoyama and Miyamoto (3) have recorded a case of lung disease in which the expectoration and the pus from a cavity in the lung contained branched threads which were "as acid-fast as *B. tuberculosis.*" A streptothrix was obtained in pure culture from the pus in the lung cavity, and the organism seemed to resemble *St. Eppingeri* more closely than any other species which has been isolated. Aoyama and Miyamoto think that the organism may be identical with that described by Buchholz in a case of streptothrix infection of the lung; this latter organism, however, was not actually isolated, and therefore it is impossible to identify it.

In addition to these cases of infection in man, in which the causative parasite has been isolated and studied, there are other cases in which the attempt to isolate the parasite on artificial media has failed. The cases recorded by Buchholz (7) and Flexner (15)

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were of this nature, and whilst the failure to obtain cultures of the parasite deprives the cases of much of their interest, these two in particular are important, as showing how closely a streptothrix infection of the lung may simulate, both in its gross morbid anatomy and in the histological changes present, a tuberculosis due to infection by Koch's *B. tuberculosis*. When, in addition, we remember that certain of these streptothrix organisms possess the same acid-fast property which was formerly thought to be a peculiarity of *B. tuberculosis*, the morphological and cultural resemblances between this latter organism and certain of the streptotricheæ acquire an increased significance.

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DESCRIPTION OF PLATE IV.

Illustrating Mr. Alexander G. R. Foulerton's and Mr. C. Price-Jones' communication on "The General Characteristics and Pathogenic Action of the Genus Streptothrix." (P. 56.)

FIG. 1.—*Streptothrix alba*: old culture showing chain sporulation.

FIG. 2.—*Streptothrix melanotica*: showing the growth of filaments from spores at the end of twenty hours' incubation. The element on the left side and upper part exhibits the development of three filaments of different length from a single spore. The element on the right side and upper part shows a single spore giving rise to a long filament, and to two minute buds or young filaments from the left side. The other elements in the figure illustrate similar processes.

FIG. 3.—*Streptothrix luteola* (Foulerton): from a six weeks old culture on maltose agar incubated at 37° C.

FIG. 4.—*Streptothrix luteola* (Foulerton): from a two weeks old culture in pepton beef broth, incubated at 37° C.

FIG. 5.—*Streptothrix hominis* (Foulerton): in the pus from a small abscess of the chest wall; stained by Gram's method.

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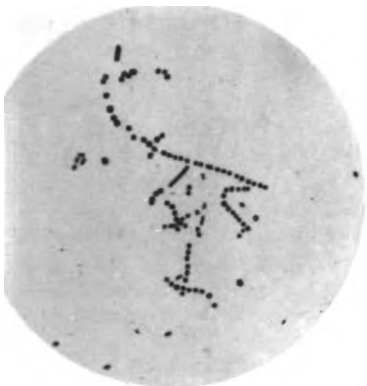

Fig. 1.

Fig. 2.

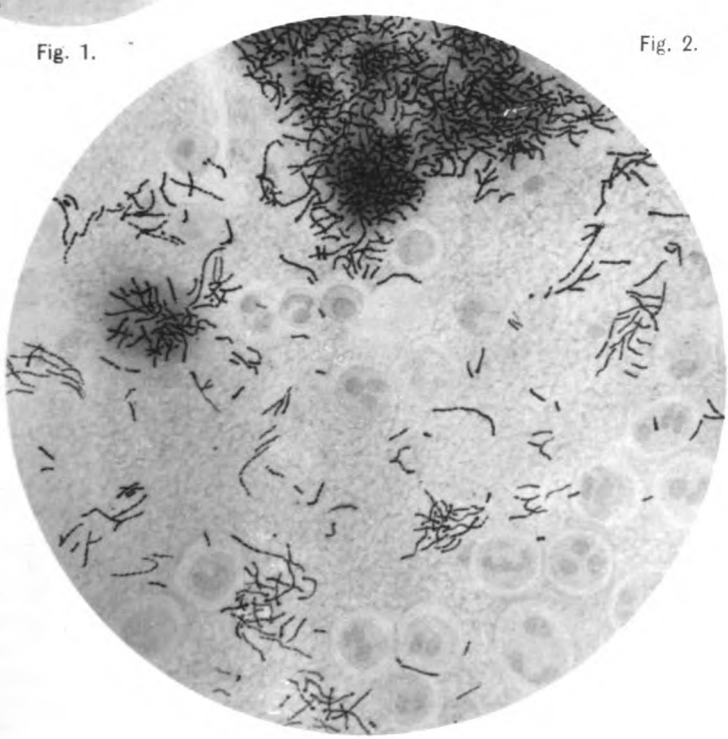

Fig. 5.

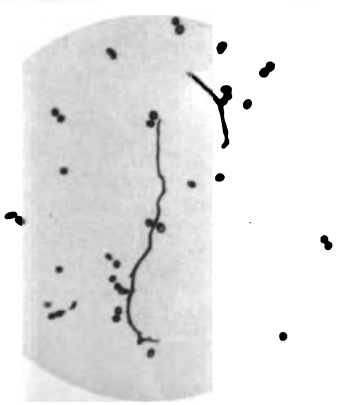

Fig. 3.

Fig. 4.

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APPENDICES.

Appendix I.—Differential table for the twenty-five species examined by the authors.

Appendix II.—Detailed description of cultures, etc., of species in Appendix I.

Appendix III.—Description of other pathogenic streptotricheæ mentioned in the paper, but not examined by the authors.

Appendix IV.—Some additional pathogenic and other species not mentioned in the paper.

APPENDIX I.

The cultures on gelatine of all species, and all the other cultures of *St. leucea saprophytica*, were incubated at a temperature of 22° C.; all other cultures were incubated at 37° C.

The starch solution used for testing diastatic action contained 1 gramme of potato starch, 1 gramme of peptone, and ·6 gramme of sodium chloride, in 100 cubic centimètres of distilled water.

When testing resistance to heat, cultures containing spores were used in every case for the experiments, of which the results are given in table; the duration of exposure at the various temperatures was thirty minutes, unless otherwise stated.

The following modification of the Ziehl-Neelsen method was used for staining purposes:—The cover-glass films were stained in warm carbol-fuchsin solution for ten minutes, were then decolourised with a 33 per cent. solution of nitric acid in water, and were finally placed in absolute alcohol for ten minutes.

Note.—The organism described below as *Streptothrix hominis* (Berestnew) does not appear to correspond exactly in cultural characters with any of those species described by Berestnew, and referred to in the paper. The organism in question was obtained from Kral, and it is probable that its original character has been modified by prolonged growth on artificial media.

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APPENDIX I.

Table of species of Streptothrix examined by the authors (A. G. R. FOULERTON *and* C. P. JONES).

No.	Species.	Growth on nutrient gelatine at 22° C.	Growth on inspissated horse-serum.	Diastatic action on starch in peptone solution.	Growth on nutrient maltose agar.	Growth on potato.	Growth in faintly alkaline litmus milk.	Resistance to heat; thermal death-point.	Staining by Ziehl-Neelsen method.
	PATHOGENIC.								
1	*Streptothrix hominis* (Berestnew)	Liquefaction	Liquefaction	No diastatic action	Growth of greyish to yellow colour; covered later by a chalky efflorescence	Growth uncertain; cultures obtained in two out of eight tubes inoculated; brownish growth covered by white chalky efflorescence	Faint acidification by end of third day; by eighth day the milk clears to a brown fluid, with alkaline reaction	60°—75° C.	Not acid-fast.
2	*Streptothrix luteola* (Foulerton)	„	No liquefaction	„	Growth is at first of greyish-white colour, frequently very thin and almost translucent, afterwards a fine white efflorescence appears on surface; or the growth may become of a light yellowish colour, no efflorescence being seen	Tuberculated growth of pale buff colour, later becoming in part or altogether covered by snowy-looking white efflorescence	Faint acidification after three days' incubation; by twentieth day milk is cleared about halfway down the tube, and by the end of four weeks appears as a clear brown fluid throughout	Survives exposure to 75° C. for 20 minutes, but is destroyed after 30 minutes' exposure to same temperature	„
3	*Streptothrix hominis* (Sabrazès and Rivière)	Liquefaction (late)	„	„	Growth of a pinkish or ochreous colour, with pinkish efflorescence	Pinkish growth with fine white efflorescence	Growth occurs; appearance and reaction of milk not altered after twenty days' incubation	45°—60° C.	Portions of the mycelium are acid-fast, but apparently not alcohol-fast.

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4	*Streptothrix bovis communis* (*Actinomyces bovis* of Bollinger and Hartz)	„	„	„	Growth at first fawn - coloured, later becoming canary - yellow, brown, or black	Raised, irregular growth of light brown, canary-yellow, greyish-black, or quite black colour	Faint acidification after the tenth day, pink coloration is then discharged, and the milk clears, becoming of a brownish colour and alkaline reaction	60°—75° C.	Not acid-fast.
5	*Streptothrix maduræ* (Vincent)	No liquefaction	„	„	Growth at first of light yellowish-white tint; later may develop pink coloration	Growth at first of a creamy yellowish-white colour; later may develop pink coloration	No obvious change occurs in the milk during the first twenty days' incubation, the liquid then becomes of a pinkish colour, and after four weeks begins to clear	45°–60° C.	„
6	*Streptothrix Eppingeri* (Eppinger)	„	„	„	Growth at first of a yellowish - white colour, then becomes of a deeper yellow to yellowish-red (burnt ochre) colour	Growth at first whitish, then becomes of a yellow to brick-red colour; fine powdery efflorescence on surface	Growth occurs; appearance and reaction of milk not altered after twenty days' incubation	60°—75° C.	Portions of the mycelium are acid-fast, but apparently not alcohol-fast.
7	*Streptothrix Nocardii* (Nocard)	„	„	„	Growth of a pale straw-colour	Buff yellowish growth	Growth occurs; appearance and reaction of milk not obviously altered after twenty days' incubation	45°—60° C.	Portions of the mycelium acid-fast and alcohol-fast.
8	*Streptothrix capræ* (Silberschmidt)	„	„	„	Growth of a dull drab colour	Growth of a light brownish to greyish colour	Slight acidification after twenty days' incubation	60°—75° C.	„
9	*Streptothrix hominis* (Foulerton)	No growth obtained on this medium	Growth very scanty; medium pitted, but no actual liquefaction	Not tested	Very slowly increasing, dry-looking whitish growth, closely resembling that of *Bacillus tuberculosis*	No growth obtained on this medium	Not tested	Not tested	Not acid-fast; only one culture examined.

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APPENDIX I.

Table of species of Streptothrix examined by the authors (A. G. R. FOULERTON *and* C. P. JONES)—*continued.*

No.	Species.	Growth on nutrient gelatine at 22° C.	Growth on inspissated horse-serum.	Diastatic action on starch in peptone solution.	Growth on nutrient maltose agar.	Growth on potato.	Growth in faintly alkaline litmus milk.	Resistance to heat; thermal death-point.	Staining by Ziehl-Neelsen method.
	SAPROPHYTIC.								
10	*Streptothrix leucea* (Foulerton)	Liquefaction	Liquefaction	Sugar production	Smooth-looking, whitish to greyish-white growth, the surface of which either shows fine white efflorescence or becomes reticulated	Light brown nodular growth, or may have appearance of a drab-coloured, moist-looking, wrinkled membrane; fine white efflorescence appears early, and after several weeks incubation becomes of drab colour	Slight acidification after three days' incubation; by eighth day red coloration is discharged, and reaction is still acid; on tenth day milk begins to clear, and by twentieth day appears clear brown throughout	70°—75° C.	Not acid-fast.
11	*Streptothrix alba* (Rossi-Doria)	,,	,,	,,	Wrinkled warty growth of greyish-white to light amber-yellow colour	Light yellowish to brownish colour; later chalky efflorescence	Slight acidification after three days' incubation; milk clears to reddish-brown fluid of alkaline reaction	60°—75° C.	,,
12	*Streptothrix alpha* (C. Price Jones)	,,	,,	,,	Smooth buff-coloured growth, which afterwards tends to become wrinkled, and is covered by a chalky efflorescence	Growth very uncertain; colour varies from pale buff to rusty brown; a chalky efflorescence appears early	Milk is coagulated; after a time a heavy sediment settles, leaving an upper layer of clear yellowish-brown fluid of an acid reaction	65°—70° C.	,,

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13	*Streptothrix leucea saprophytica* (Foulerton)	,,	,,	,,	Smooth whitish growth, which becomes completely covered with dead white efflorescence	Light brownish nodular growth, which is quickly covered by snowy white efflorescence	No change in appearance or reaction of milk up to eighth day; colour is then discharged, and milk clears very slowly to darkish brown fluid	45°—60° C.	,,
14	*Streptothrix cinereo-nigra arenatica* (Berestnew)	,,	,,	No diastatic action	Growth of light yellow to grey colour; scanty efflorescence	Growth is entirely covered with chalky efflorescence from the first	Faint acidification after three days' incubation; milk then clears to brown liquid of alkaline reaction	Destroyed by exposure to 45° C. for 30 minutes	,,
15	*Streptothrix violacea* (Rossi-Doria)	,,	,,	,,	Slightly raised creamy-looking growth which is soon covered by a chalky efflorescence; the growth beneath the efflorescence becomes of a smoky brown colour, and the tint gradually deepens	No growth was obtained on any of ten tubes inoculated	,,	,,	,,
16	*Streptothrix orangica*	,,	,,	,,	Growth at first is of a light amber-yellow colour, and is quickly covered with a chalky efflorescence, under which the colour develops to a deeper yellow or orange-red. Culture has a fragrant, aromatic odour	Growth uncertain, obtained on only one out of eight tubes inoculated, and then presented a coarse, wrinkled surface, with a fine efflorescence covering it	Faint acidification; milk clears quickly, and by eighth day is a clear brown liquid of alkaline reaction	,,	,,

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APPENDIX I.

Table of species of Streptothrix examined by the authors (A. G. R. FOULERTON *and* C. P. JONES)—*continued.*

No.	Species.	Growth on nutrient gelatine at 22° C.	Growth on inspissated horse serum.	Diastatic action on starch in peptone solution.	Growth on nutrient maltose agar.	Growth on potato.	Growth in faintly alkaline litmus milk.	Resistance to heat; thermal death-point.	Staining by Ziehl-Neelsen method.
17	*Streptothrix erythrea* (Foulerton)	Liquefaction	Liquefaction	No diastatic action	Heaped-up growth without any tendency to spread over surface of medium; of a bright red colour; resembles small masses of coral	Growth very scanty on this medium; is of bright red colour as on maltose agar	Growth occurs; no change in reaction or appearance of milk after four weeks' incubation	Destroyed by exposure to 45° C. for 30 minutes	Not acid-fast.
18	*Streptothrix beta* (C. Price Jones)	„	„	„	Growth of buff colour, later coloured with chalky efflorescence	Growth very uncertain on this medium; when it occurs is of a buff yellow colour, and yields a gritty sensation when touched with platinum wire	Faint acidification after three days' incubation; red coloration is then discharged, and milk clears to brown liquid of alkaline reaction with granular sediment	50°—55° C.	„
19	*Streptothrix nigra* (Rossi-Doria)	„	No liquefaction	Sugar production	Growth of a light grey colour which darkens somewhat, and later is covered with chalky efflorescence	Drab or buff-coloured growth; later covered with chalky efflorescence of a yellowish tint	Faint acidification after three days' incubation; red coloration is discharged, and milk clears to dark brown liquid of alkaline reaction	60°—75° C.	„
20	*Streptothrix nigrescens* (*Cladothrix dichotoma* of Cohn and Mace)	„	„	„	Growth of light grey colour, later is covered with chalky efflorescence	Growth varies in colour from drab to chrome or orange-yellow; becomes covered with a dead white chalky efflorescence	Faint acidification; red coloration is discharged, and milk clears from above downwards to liquid with alkaline reaction, which at first is brown, and gradually darkens to quite black	50°—55° C.	„

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21	*Streptothrix odorifera* (Rullmann)	„	„	„	Raised, drab-coloured, semi-translucent growth, the surface of which later becomes reticulated	Growth was obtained on only one out of eight tubes inoculated	Growth occurs; at the end of four weeks the tint of the liquid is pinkish; there is no sign of clearing	Destroyed by an exposure to a temperature of 45° C. for 30 minutes	Not acid-fast.
22	*Streptothrix graminearium* (Berestnew)	„	„	No diastatic action	Growth from the first is covered with chalky efflorescence showing a delicate pink tinge	Growth resembles that on maltose agar	Faint acidification; red coloration is discharged, and milk clears very slowly from above downwards, ultimately becoming of a deep brown or black colour	Destroyed by exposure to 45° C. for 30 minutes	„
23	*Streptothrix Gabritschewskii* (Berestnew)	Liquefaction (late)	„	„	Growth of a chocolate-red colour, with fine, powdery, white efflorescence	Reddish-brown growth with fine efflorescence	Growth occurs; appearance and reaction of milk not altered after twenty days' incubation	45°—60° C.	„
24	*Streptothrix melanotica* (C. Price Jones)	No liquefaction	No liquefaction	„	Growth is at first of a buff colour, later becomes covered with a chalky efflorescence, and appears of a greyish colour by reflected light, but almost black by transmitted light	Growth at first of a buff colour, later becomes covered with a chalky efflorescence, appearing on the surface of a greyish colour, but is black beneath	Faint acidification after three days' incubation; the red coloration is then discharged, and the milk clears to a brown liquid of acid reaction, with a fine granular sediment	60°—65° C.	„
25	*Streptothrix pluricolor* (Terni)	„	„	„	Growth has a pink powdery-looking surface	Growth varies in colour from grey to rusty red, and shows in places a fine white efflorescence	No change in appearance or reaction of milk after twenty days' incubation	45°—60° C.	„

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APPENDIX II.

Detailed description of cultures of species examined by the authors.

1. **Streptothrix hominis,** syn. *Actinomyces hominis* (Berestnew).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Aërobe; very scanty growth under anaërobic conditions.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 72 hours; a light buff-coloured mass sinking into medium, which is completely liquefied by tenth day. Stab culture: flocculent expansion at the top of gelatine, and a feathery growth along the track; no pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 48 hours as small discoid greyish-yellow colonies, with waxy surface, later covered by chalky efflorescence; slight brown (smoky) pigmentation of medium by tenth day.

On *inspissated horse-serum at* 37° *C.*—Growth appears after 24 hours; the medium becomes completely liquefied, and shows slight brown pigmentation.

On *potato at* 37° *C.*—Growth uncertain, only two cultures obtained out of eight tubes inoculated; appears about tenth day; slightly raised, wrinkled, brown growth, covered more or less by chalky efflorescence; brown pigmentation and slight erosion of medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours; discoid flocculent colonies at bottom of tube; later, surface growth of fine cohering colonies; smoky tinting of medium by tenth day.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is pinkened; by eighth day it has become a clear, brown alkaline liquid.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist exposure to 60° C. for 30 minutes, but are killed by exposure to 75° C. for same period.

Pathogenicity for lower animals.—(?).

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2. **Streptothrix luteola** (Foulerton).

Isolated from a case of sloughing keratitis.

STAINING CHARACTERISTICS.—Stains well by Gram's method in young cultures; cultures up to three months old show no acid-fast portions when stained by the Ziehl-Neelsen method.

CULTURAL CHARACTERISTICS.—Grows freely in presence of oxygen, very scanty growth under anaërobic conditions; on all media, except potato, growth is distinctly more active at 37° C. than at 22° C.; old cultures, especially those in peptone beef broth, have a faintly feculent odour.

On *gelatine at 22° C.*—Streak culture: obvious growth is seen on third day, at first of an opaque white appearance, later may show a very faint yellowish tinge. Growth sinks slowly into the medium, which gradually liquefies. Stab culture: growth occurs along track of needle in the form of superimposed discoid colonies, which have a somewhat flocculent appearance. After four weeks' incubation the gelatine of an ordinary stab culture is liquefied to about one third of its depth; the resulting fluid is freely mobile, and for several weeks, at any rate, shows no sign of pigmentation, but after prolonged incubation the fluid may become very slightly darkened.

On *peptone-maltose agar.*—After 24 hours' incubation at 37° C. there is some indication of growth; at 22° C. no obvious growth occurs within this period. After 72 hours' incubation at 37° C. there is a fair amount of growth, and rather less after incubation at 22° C. The growth, at first of a faint drab or whitish tint, after longer incubation becomes usually of a faint yellowish colour. Cultures may yield a free formation of aërial hyphæ, giving a snowy appearance to the surface of the growth, or the surface may assume a reticulated appearance, without any efflorescence.

On *inspissated horse-serum.*—Growth is comparatively scanty on this medium, appearing after 72 hours' incubation at 37° C. At the end of twenty-eight days' incubation at 37° C. there is a dry wrinkled drab-coloured growth, which has sunk slightly into the medium; beyond this sinking into the medium there is no indication of liquefaction.

On *potato.*—Growth on this medium is equal at temperature 37° C. and 22° C.; at the end of 48 hours' growth appears as a brownish or faintly yellowish stain on the medium; later, growth usually assumes a "coffee with milk" colour; there is no pigmentation or erosion of the medium. Surface efflorescence is seen only in cultures incubated at 37° C., and not in cultures at 22° C.

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In *peptone beef broth.*—After 48 hours' incubation at 37° C. the appearance of some filmy growth is seen at the bottom of the tube; in older cultures growth appears as flocculent, more or less discoid colonies. There is no pigmentation of the broth after incubation for eight weeks. There is no marked tendency to surface growth, as seen with some species.

In *alkaline litmus milk.*—Medium at end of 72 hours' incubation at 37° C. is of a faint pink colour, but there is no coagulation. The pink colour changes to a dirty white, and the milk clears gradually from the surface downwards, becoming at last of a brown colour.

Growth on *peptone agar* is about equal to that on peptone-maltose agar; growth on glycerine-agar (1 per cent. glycerine) is less free than it is on either of the two preceding media.

Diastatic action.—No action of the sort is manifested within fourteen days' incubation at 37° C.

Resistance to heat.—Sporulating cultures resist exposure to moist heat at 70° C. for 20 minutes, but are destroyed by an exposure to the same temperature for 30 minutes.

Pathogenicity for lower animals.—Not found pathogenic for rabbits (intra-venous and intra-peritoneal inoculation), for guinea-pigs (intra-peritoneal inoculation), or for tame mice (intra-peritoneal and sub-cutaneous inoculation).

3. **Streptothrix hominis** (Sabrazès and Rivière).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show acid-fast portions, but these are not alcohol-fast.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after fifth day; slightly raised, white powdery growth, with a faint pink tint; no liquefaction of medium. Stab culture: a series of fine, faint pink colonies along track; no pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 48 hours; small circular pinkish or ochreous colonies, growing only slightly into the medium; no pigmentation of medium.

On *inspissated horse-serum at* 37° *C.*—Growth appears after fourth day; no liquefaction or pigmentation of medium.

On *potato at* 37° *C.*—Growth appears after third day as slightly raised, granular pink layer, covered here and there by a fine white efflorescence; no pigmentation or erosion of medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as discrete discoid colonies and flocculent masses at bottom of tube.

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In *alkaline litmus milk at* 37° *C.*—Growth occurs, but reaction and appearance of the milk is not obviously altered after twenty days.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist exposure to 45° C. for 30 minutes, but killed by exposure to 60° C. for same period.

Pathogenicity.—Not pathogenic for rabbit, guinea-pig, or dog (Sabrazès and Rivière).

Note.—Sabrazès and Rivière state that the organism is essentially aërobe; that the optimum temperature for growth is 38° C., the limits being 16° to 40° C.; that it is able to saponify fatty bodies, and that in assimilating glycerine it develops at the expense of the fatty matters; that it ferments dextrose, maltose, and lactose; that it produces a yellow pigment soluble in ether, insoluble in water, and not acted upon by acids or bases; and that when grown in pure oxygen the medium is not pigmented, but the colonies are of a brownish colour.

4. **Streptothrix bovis communis** (*Actinomyces bovis* of Bollinger and Harz).

STAINING CHARACTERISTICS.—Cultures stained by the Ziehl-Neelsen method show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Aërobe; very slight growth under anaërobic conditions.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 96 hours, a yellowish-white growth; slow liquefaction of medium commences about seventh day. Stab culture: growth appears as a series of superimposed whitish or yellowish opaque discs along the track of the needle; no pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 48 hours as small, discrete, fawn-coloured colonies, with smooth, waxy surface, later becoming canary-yellow, dark brown, or black; medium may be slightly darkened.

On *inspissated horse-serum at* 37° *C.*—Growth slow, and not extensive at any time; no liquefaction of medium.

On *potato at* 37° *C.*—Appears after 48 hours, raised irregular growth of various colours, brown, canary-yellow, greyish-black, or quite black; more or less pigmentation and erosion of the medium occurs.

In *peptone beef broth at* 37° *C.*—Whitish, opaque, more or less cohering colonies, often with slightly brown pigmented centres at bottom of tube; surface growth rare; no pigmentation of medium.

In *alkaline litmus milk at* 37° *C.*—After ten days medium is pinkened

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and its colour discharged; by eighteenth day it has become a clear, brown, alkaline liquid.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist exposure to 60° C. for 30 minutes, but killed by exposure to 75° C. for same period.

Pathogenicity for lower animals.—Pathogenic for guinea-pigs and rabbits.

Note.—Cultures of *Actinomyces sulphureus* and *Actinomyces hominis* (Affanassiew), obtained from Kral, survived exposure to 45° C. for 30 minutes, but killed by exposure to 60° C. for same period.

5. **Streptothrix Maduræ** (Vincent).

STAINING CHARACTERISTICS.—Cultures up to fourteen weeks old, stained by the Ziehl-Neelsen method, showed no acid-fast portions.

CULTURAL CHARACTERISTICS.—Aërobe; very slight growth under anaërobic conditions.

On *gelatine at 22° C.*—Streak culture: growth appears after eight to twenty-one days, always scanty, as opaque, whitish, raised, more or less discrete colonies; no liquefaction or pigmentation of medium. Stab culture: series of superimposed flattened, globular, opaque, whitish colonies occur along the track of the needle.

On *maltose-peptone agar at* 37° *C.*—Growth disappears after eighth day; small, discrete, yellowish-white colonies, with waxy, wrinkled surface, later often developing pink pigment; slight brown tinting of medium in old cultures.

On *inspissated horse-serum at* 37° *C.*—Growth slow and scanty; no pigmentation or liquefaction of medium.

On *potato at* 37° *C.*—Growth appears after 72 hours as heaped-up irregular mass of creamy yellowish-white colour, often showing patches of pink coloration; no pigmentation or erosion of medium.

In *peptone beef broth at* 37° *C.*—Growth appears as opaque white, globular, more or less cohering colonies at bottom of tube; surface growth rare; no pigmentation of medium.

In *alkaline litmus milk* at 37° *C.*—Growth occurs; no obvious change happens in the milk during the first twenty days' incubation, the liquid then becomes of a pinkish colour, and after four weeks begins to clear.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 45° C.

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for 30 minutes, but killed by an exposure to 60° C. for the same period.

Pathogenicity for lower animals.—The inoculation of cats, rabbits, guinea-pigs, and mice produced nothing more than small nodules at the site of injection, and these disappeared (Vincent). Nocard carried out intra-peritoneal, intra-venous, and subcutaneous inoculations of dogs, sheep, rabbits, guinea-pigs, fowls, and pigeons; his results were negative in every case.

6. **Streptothrix Eppingeri** (Eppinger).

STAINING CHARACTERISTICS.—Cultures of two to three months old, stained by Ziehl-Neelsen method, show portions which are acid-fast but not alcohol-fast.

CULTURAL CHARACTERISTICS.—Aërobe; very slight growth under anaërobic conditions.

On *gelatine at* 22° *C.*—Streak culture: growth appears after sixth day as a slightly raised wrinkled layer with deep orange centre and paler, often thinned out, periphery; no liquefaction or pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after fifth day as slightly raised, granular, yellowish-white mass, with pale, flat, polished periphery; later the growth assumes a deeper yellow to burnt ochre colour; no pigmentation of medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 24 hours; no liquefaction or pigmentation of medium.

On *potato at* 37° *C.*—Growth appears after 48 hours as a granular layer, at first white, becoming yellow to brick-red, and later covered by fine white powdery efflorescence, the culture resembling a "sugar almond."

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as small white granules forming a pellicle, and adhering to sides of tube; some portions fall to bottom of tube; no pigmentation of medium.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is pinkened; by eighth day the colour is discharged, and milk has become alkaline; but even after a month's incubation the medium does not clear.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 60° C. for 30 minutes, but are killed by exposure to 75° C. for the same period.

Pathogenicity for lower animals.—Not pathogenic for white mice

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(eleven experiments). Three rabbits inoculated subcutaneously recovered after developing temporary local swellings; one rabbit inoculated in anterior chamber of eye developed a nodule on the iris, but no general infection; one rabbit inoculated in the kidney, and another intra-venously, died on seventh and fifth days respectively; the muscles and organs generally of these two animals showed numbers of yellowish-white nodules, from which the streptothrix was obtained in pure culture. Two guinea-pigs inoculated intra-peritoneally died on eighteenth and twenty-fourth days with similar *post-mortem* appearance (Eppinger).

Note.—Eppinger described the organism as a cladothrix, stating that it was clear that the lateral branches had no organic connection with the parent threads. The organism is now, however, definitely placed among the streptotricheæ, and the culture which we have examined, and which appears to correspond with Eppinger's description in most of the cultural and other details, is a typical streptothrix. Eppinger also states that the short "bacillary" forms are motile; we have not, however, been able to distinguish any evidence of transitive motility in the older cultures containing short segments which we have examined.

7. **Streptothrix Nocardii** (Nocard).

STAINING CHARACTERISTICS.—Cultures from nine days to three months old, stained by Ziehl-Neelsen method, showed many acid-fast portions, and these were also alcohol-fast.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after four days as a fine, white opacity, with uneven surface. Stab culture: slightly raised knob at the top of gelatine and a fine filmy growth along the track of the needle; no liquefaction or pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Appears after 48 hours; pale straw-coloured growth, with dull, flattened, granular surface; no pigmentation of medium.

On *inspissated horse serum at* 37° *C.*—Very slow growth; no liquefaction of medium.

On *potato at* 37° *C.*—Appears after 48 hours; buff yellow granular growth; no pigmentation or erosion of medium.

In *peptone beef broth at* 37° *C.*—Appears after 24 hours; greyish, flocculent mass at bottom of tube; no pigmentation of medium (growth does not alter the reaction of neutral or alkaline broth, even when the latter contains glucose, Nocard).

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In *alkaline litmus milk at* 37° *C.*—Growth occurs, but reaction and appearance of medium are not obviously altered after twenty days' incubation.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist exposure to 45° C. for 30 minutes, but are killed by exposure to 60° C. for same period (cultures resist exposure to 65° C. for 15 minutes, but are killed by exposure to 70° C. for ten minutes, Nocard).

Pathogenicity for lower animals.—Rabbits, dogs, cats, horses, and asses are not affected by either intra-peritoneal or intra-venous injection. In guinea-pigs intra-peritoneal or intra-venous injection causes constantly, within nine to twenty days, a miliary tuberculosis similar to that produced by *Bacillus tuberculosis*. The abdominal viscera are widely invaded, the thoracic viscera never. In the rabbit, dog, horse, and ass subcutaneous inoculation causes local abscess which discharges and heals. In the guinea-pig, sheep, and ox an ulcer remains at site of inoculation, and lymphatic infection follows. In guinea-pigs the course of the disease was slow; one died after fifty-four days, and fifteen killed between one and five months after inoculation showed no lesions beyond those in the lymphatic vessels and glands in the neighbourhood of the site of inoculation. In the lymphatic abscess numerous organisms which had preserved their normal virulence were found. In sheep and in oxen a series of abscesses developed about the site of inoculation, but the disease was, as in the natural conditions, when the animal may live for several years, an extremely chronic one. The organism remained localised in the lymphatics, and showed no tendency to cause a general infection (Nocard).

8. **Streptothrix capræ** (Silberschmidt).

STAINING CHARACTERISTICS.—Cultures of three months old, stained by the Ziehl-Neelsen method, showed many acid-fast portions, and these were also alcohol-fast.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears on third day as a slightly raised mass; the surface is covered with chalky efflorescence, and has a faint pinkish tint. Viewed from under-surface the growth has a wrinkled appearance and definite pink tinge (colonies have a brownish centre with clearer periphery, Silberschmidt). Stab culture: small, chalky knob at the top, and fine, filmy growth, with pinkish tinge at upper end, along the track of the needle; no liquefaction or pigmentation of medium.

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On *maltose-peptone agar at* 37° *C.*—Growth appears after 24 hours as a spreading drab-coloured layer; surface partly dull, and with powdery appearance; slight darkening of medium in old cultures.

On *inspissated horse serum at* 37° *C.*—Free growth; no liquefaction of medium.

On *potato at* 37° *C.*—Appears after 24 hours; slightly raised, finely granular growth, brown to grey in colour and partly covered with white efflorescence; brown tingeing of potato but no erosion (potato growth is of "brun rose" colour, which is less marked when the tube is capped, Silberschmidt).

In *peptone beef broth at* 37° *C.*—Small, isolated, and coherent flocculent colonies at surface and at bottom of medium; no pigmentation of the broth.

In *alkaline litmus milk at* 37° *C.*—Growth occurs on surface (forming a film of "blanc rose" colour, Silberschmidt), but after twenty days' incubation the milk shows no change, beyond a very slight pinking (coagulation does not occur, Silberschmidt).

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist exposure to 60° C. for 30 minutes, but are killed by exposure to 75° C. for same period.

Pathogenicity for lower animals.—Subcutaneous inoculation into rabbits produces a local abscess; intra-venous inoculation produced nodules in various organs; the pulmonary nodules present giant-cells, and caseate rapidly. Four mice were inoculated subcutaneously: two had local abscesses, from which the organism was recovered; the other two suffered no effects. Two mice received intra-peritoneal injections and remained well. In the guinea-pig subcutaneous inoculation in one case was followed by death on eighteenth day; there were numerous suppurating nodules in the parietal peritoneum, mesentery, diaphragm, liver, kidney, and spleen. From these nodules cultures were obtained. Two other guinea-pigs recovered, with a local abscess, after a similar inoculation, but no other lesions. Three guinea-pigs received intra-peritoneal injections: one recovered, the other two died on the sixth and thirty-first days respectively. In these there were found very numerous miliary nodules on the diaphragm, surface of liver, mesentery, serous coat of stomach, and on the testicles. (Silberschmidt.)

9. **Streptothrix hominis** (Foulerton).

Isolated from a case of pulmonary infection in a woman.

STAINING CHARACTERISTICS.—Cultures stain well by Gram's method. A three months old culture from glycerine-peptone agar

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showed no acid-fast portions when stained by the Ziehl-Neelsen method.

CULTURAL CHARACTERISTICS.—Growth was obtained in peptone beef broth and on solid media under ordinary aërobic conditions; no growth occurred on tubes of peptone agar and glycerine-peptone agar incubated under anaërobic conditions. Growth is more active at 37° C. than at 22° C.

On *peptone agar*.—Growth very slow and scanty; after several weeks' incubation small whitish, heaped-up, dry-looking colonies, resembling somewhat the growth of *B. tuberculosis*, are seen.

On *glycerine agar* and *maltose-peptone agar*.—The amount of growth is very much the same as in the last case, and of much the same appearance.

On *inspissated horse serum and inspissated ox serum*.—Growth is very scanty; the colonies sink slightly into the medium.

On *potato*.—No growth was obtained.

In *peptone beef broth*.—Small globular colonies appear in the depth of the broth after about six days' incubation at 37° C. These do not increase much in size, and after four weeks' incubation are not much larger than a pin's head; there is a tendency for the colonies to cohere in flocculent masses. The growth is whitish in colour.

Pathogenicity for lower animals.—Two rabbits received intraperitoneal injections of broth cultures, but there were no obvious effects.

10. **Streptothrix leucea** (Foulerton).

Isolated from sewage effluents and from water.

STAINING CHARACTERISTICS.—Stains well by Gram's method; no portions acid-fast when stained by Ziehl-Neelsen method.

CULTURAL CHARACTERISTICS.—Is an aërobic organism, very scanty growth occurring under anaërobic conditions. Growth is rather more active at 37° C. than at 22° C. Cultures have a strong mouldy smell.

On *gelatine at 22° C.*—Streak culture: obvious growth after 48 hours' incubation; liquefaction of the medium begins after about four days; the gelatine is not pigmented. Stab culture: after 72 hours' incubation growth has taken place along the track of the needle, and appears as a series of superimposed, flattened, circular colonies, diminishing progressively in circumference from the surface downwards, the surface colony being of a greyish-white colour. Liquefaction appears on fourth or fifth day, and extends slowly downwards.

On *peptone-maltose agar at 37° C.*—Growth appears after about 36 hours' incubation, presenting a greyish-white, more or less shining

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surface; the under surface becomes coarsely wrinkled and appears brownish by transmitted light. After between four and six weeks' incubation the medium may show a very faint reddish tinge. The formation of aërial hyphæ produces the appearance of a white, chalky efflorescence.

Growth on *peptone agar and glucose-peptone agar* is about the same as on last, but the reddish tingeing of the medium does not occur. Growth on glycerine-peptone agar is less free than on the preceding.

On *inspissated horse serum and inspissated ox serum.*—On these media growth is scanty as compared with that on maltose agar; the growth at first sinks slowly into the medium, and afterwards complete peptonisation occurs.

On *potato.*—Growth is obvious after about 36 hours at 37° C., appearing as a raised surface which frequently has a wrinkled appearance, and is of a drab to light brownish colour. A fine white chalky efflorescence, which afterwards darkens, appears about the eighth day, or earlier. The medium gradually darkens in colour, and by the fourteenth day may be of a rich chocolate-brown colour; a certain amount of erosion of the medium occurs.

In *peptone beef broth.*—Growth occurs as largish discoid colonies, which in time cohere to form flocculent masses at the bottom of the tube. A complete surface veil, showing chalky efflorescence, sometimes forms.

In *alkaline litmus milk.*—Preliminary pinking of the milk occurs without any coagulation. After about eight days' incubation at 37° C. the colour is discharged, and the milk clears gradually to a dark brown fluid.

Diastatic action.—All the starch in the solution is converted within four days' incubation at 37° C.

Resistance to heat.—Sporulating cultures survive exposure to moist heat at 70° C. for 20 minutes, and are destroyed by exposure to temperature of 75° C. for same length of time.

Pathogenicity for lower animals.—Not pathogenic for rabbits (intra-venous and intra-peritoneal inoculation), guinea-pigs (intra-peritoneal and subcutaneous inoculation), or for tame mice (intra-peritoneal and subcutaneous inoculation).

11. **Streptothrix alba** (Rossi-Doria).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Aërobe; very slight growth under anaërobic conditions.

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On *gelatine at* 22° *C.*—Streak culture: growth appears after 24 hours as a yellowish-white expansion sinking into medium. Stab culture: at the top a white flocculent expansion with a brown centre, floating on the liquefied gelatine; along the track a fine pyramidal "fir tree" growth. There is slow but complete liquefaction, and no pigmentation of the medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears within 48 hours as a wrinkled warty layer, with waxy surface and of greyish-white to light amber-yellow colour, which later is more or less covered with chalky efflorescence; no pigmentation of medium.

On *inspissated horse serum at* 37° *C.*—Appears after 24 hours; there is a brown pigmentation and complete liquefaction of medium (ten to eighteen days).

On *potato at* 37° *C.*—Growth appears after 48 hours as a slightly raised, finely wrinkled, yellow to brown membranous layer, which is later more or less covered by chalky efflorescence; there is a brown pigmentation and some erosion of the medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as discrete opaque white flocculent colonies at bottom of the tube; no pigmentation of medium.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is pinkened, by eighteenth to twentieth day it has become a clear red-brown alkaline liquid.

Diastatic action.—Manifested after three days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 60° C. for 30 minutes, but are killed by an exposure to 75° C. for the same period.

Pathogenicity for lower animals.—(?).

12. **Streptothrix alpha** (C. Price Jones).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Grows well under both aërobic and anaërobic conditions.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 48 hours as a buff-coloured expansion sinking into medium. Stab culture: at top a small expansion sinking into cup of liquefied medium, and a series of buff-coloured superimposed discs along track of needle. The medium is slowly but completely liquefied, there is no pigmentation of the medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 24 hours

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as slightly raised buff-coloured discs, with smooth surface, which later becomes wrinkled and covered by chalky efflorescence; there is late brownish coloration of medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 24 hours as a grey to brown wrinkled warty layer; the medium is rapidly liquefied; there is no pigmentation of medium.

On *potato at* 37° *C.*—Growth uncertain; appears after 48 hours as a pale buff to rusty brown lichenous or warty mass, which later is more or less covered by chalky efflorescence. After two to three weeks the potato becomes variously discoloured (brown) and much eroded.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as discrete white fluffy colonies at bottom of tube; later, surface growth; there is a faint brown pigmentation of the medium.

In *alkaline litmus milk at* 37° *C.*—Milk is curdled throughout; later, eighth to tenth day, a heavy deposit settles, leaving a clear yellow-brown acid liquid.

Diastatic action.—Was manifested after seven days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 65° C. for 30 minutes, but are killed by an exposure to 70° C. for the same period.

Pathogenicity for lower animals.—Not pathogenic for rabbits, guinea-pigs, or mice.

13. **Streptothrix leucea saprophytica** (Foulerton).

Isolated from water.

STAINING CHARACTERISTICS.—Young cultures stain well by Gram's method; cultures up to three months old show no acid-fast portions when stained by the Ziehl-Neelsen method.

CULTURAL CHARACTERISTICS.—Grows freely under either aërobic or anaërobic conditions, at temperature 22° C.; no growth whatever occurs at temperature 37° C. Cultures have a strong mouldy smell; are capable of a certain amount of growth in sterilised tap water.

On *gelatine at* 22° *C.*—Streak culture: growth appears after from 36 to 48 hours' incubation; liquefaction commences a little later, and is rather slow; growth is of opaque white appearance, and there is no pigmentation of the liquefied gelatine. Stab culture: growth appears as a series of superimposed discrete whitish colonies, which diminish in circumference from near to the surface downwards; liquefaction commences on the surface of the gelatine after about 98 hours' incubation, and progresses slowly downwards.

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On *peptone-maltose agar at* 22° *C.*—Growth appears after about 36 hours' incubation; it has the appearance of a thin, smooth, greyish-white film, which usually becomes covered with a white efflorescence.

On *inspissated horse serum and inspissated ox serum at* 22° *C.*—Growth appears as a smooth, greyish layer, which afterwards shows a white efflorescence on its surface; peptonisation of the serum is obvious rather late, after about fourteen days' incubation.

On *potato at* 22° *C.*—Growth is obvious after between 48 and 72 hours' incubation, is of a brownish colour, and has a granular, or finely nodular, surface. Beyond the growing margin there is a narrow zone in which the potato is of a lighter colour than elsewhere. A snowy white efflorescence soon covers the surface of the growth. The medium is not pigmented.

In *peptone beef broth at* 22° *C.*—Growth occurs after about 48 hours in the form of white flocculent masses at the bottom of the tube; free surface growth may also occur; there is no pigmentation of the broth.

In *alkaline litmus milk.*—There is no change in the colour of the medium until about the eighth day, after which the blue of the litmus is gradually discharged, and the milk clears to a dark brown fluid.

Diastatic action.—Manifest within seven days.

Pathogenic action on lower animals.—Inoculation of rabbits, guinea-pigs, and tame mice with this streptothrix is without any obvious effect. (This organism possibly corresponds with *Streptothrix nivea* which is referred to by some writers.)

14. **Streptothrix cinereo-nigra aromatica** (Berestnew).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 24 hours as a whitish expansion sinking into medium. Stab culture: slight whitish growth along track; the medium is slowly liquefied; no pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 48 hours as a flat warty layer with smooth varnished surface of light yellow to grey colour; no pigmentation of medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 24 hours; there is no pigmentation; complete liquefaction of medium after eighteen days.

On *potato at* 37° *C.*—Growth appears about ninth day, but is uncertain, subcultures frequently failing; a raised nodular growth,

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covered in places with chalky efflorescence. There is a dark brown to black pigmentation but no erosion of medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as small flocculent coherent colonies at bottom of tube; no pigmentation of medium after ten days' growth.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is faintly pinkened, by twentieth day it has become a clear brown alkaline liquid.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures are killed by an exposure to 45° C. for 30 minutes.

15. **Streptothrix violacea** (Rossi-Doria).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 24 hours; a white beaded growth sinking into medium. Stab culture: a deep funnelling at the top and a series of fine white beads along the track of the needle. There is slow but complete liquefaction of medium; within ten days there is no pigmentation of the gelatine, but later it assumes a light purple-brown colour.

On *maltose-peptone agar at* 37° *C.*—Appears after 48 hours; a slightly raised mass of confluent discoid colonies of creamy white colour, later covered by thick chalky efflorescence. The under surface of the growth has a smoky brown colour; there is a violet brown pigmentation of the medium.

On *inspissated horse serum at* 37° *C.*—Appears after 48 hours; the medium is liquefied, but there is no pigmentation after eighteen days' incubation.

On *potato at* 37° *C.*—No growth obtained.

In *peptone beef broth at* 37° *C.*—Growth appears after 72 hours as grey flocculent colonies at bottom of tube; there is no pigmentation after ten days' incubation, but later, at room temperature, the medium assumes a light purple-brown colour.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is pinkened, and by eighth day it has become a clear brown alkaline liquid.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures are killed by an exposure to 45° C. for 30 minutes.

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16. **Streptothrix orangica** (Berestnew).

STAINING CHARACTERISTICS.—Cultures up to six weeks old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 24 hours as a spreading white layer covered by chalky efflorescence. Stab culture: a feathery growth along track of the needle. There is complete liquefaction but no pigmentation of the medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 48 hours as a spreading wrinkled light amber-coloured layer, with waxy surface, soon covered by fine chalky efflorescence; the under surface has a yellow to orange-red colour, which is especially marked in old cultures that have stood at room temperature. The culture has a fragrant aromatic odour; there is no pigmentation of the medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 24 hours; there is complete liquefaction but no pigmentation of medium.

On *potato at* 37° *C.*—Growth uncertain, only one subculture obtained out of eight tubes inoculated, appearing after 48 hours as a coarsely wrinkled raised surface, covered by fine powdery efflorescence; there is a light brown pigmentation but no erosion of the medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as discrete colonies and flocculent masses at bottom of tube; there is no pigmentation of medium.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is pinkened, and by eighth day it has become a clear brown alkaline liquid.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures are killed by an exposure to 45° C. for thirty minutes.

17. **Streptothrix erythrea** (Foulerton).

This organism was found by Dr. Charles Slater on some culture-tubes of horse serum which had gone through the ordinary process of sterilisation. Dr. John Wilkinson has informed us that he has met with an apparently identical streptothrix in some tubes of the fluid from a case of chronic rheumatoid arthritis. In both cases the organism apparently occurred as an accidental contamination from the air.

STAINING CHARACTERISTICS.—Stains well by Gram's method; cultures up to three months old show no acid-fast portions when stained by the Ziehl-Neelsen method.

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CULTURAL CHARACTERISTICS.—Grows in presence of oxygen; no growth occurs under strict anaërobic conditions. The organism yields at temperatures 37° C. and 22° C. a rather scanty growth on most media; growth on similar media is rather more active at the higher temperature. On all media the growth has a bright red colour.

On *gelatine at 22° C.*—Streak culture: growth occurs as small isolated, red colonies; these sink slowly into the medium, which is slowly liquefied to a thick viscid fluid. Stab culture: growth occurs to a limited extent along the stab in the form of small globular colonies; the gelatine is slowly liquefied; there is no pigmentation of the medium.

On *peptone-maltose agar.*—Growth on this medium is comparatively free. At the end of about 96 hours' incubation some evidence of growth can be seen; the growth continues very slowly for several weeks, and at the end of a month may appear as heaped-up, rough-looking, friable colonies of a bright red colour, and rather smaller than a split pea. There is no pigmentation of the medium.

On *plain peptone agar and on glycerine-peptone agar.*—Growth is distinctly less active than on the preceding.

On *inspissated horse serum and inspissated ox serum.*—On these media growth is comparatively more free than is the case with most of the other streptotricheæ examined. At the end of 48 hours distinct growth can be seen at temperatures 37° C. and 22° C.; at the end of 72 hours' incubation at 37° C., commencing peptonisation of the medium is obvious at 22° C.; the first signs of peptonisation are noticeable about 24 hours later. Growth appears as a thin reddish layer, which gradually sinks into the medium.

On *potato.*—On this medium the organism retains its vitality for a considerable time, but no obvious growth occurs.

In *peptone beef broth.*—Growth occurs in the form of small colonies at the bottom of the tube, resembling in appearance small uric acid concretions; a few of the colonies may adhere to the side of the tube; there is no surface growth. In a few out of many cultures in broth, the small red colonies became enveloped by a considerable whitish flocculent expansion, which consisted of branching threads resembling microscopically those of the original red colony.

In *alkaline litmus milk.*—A small amount of growth occurs. The appearance of the medium is not materially altered after four weeks' incubation at 37° C.

Diastatic action.—No diastatic action occurs within fourteen days' incubation at 37° C.

Resistance to heat.—Sporulating cultures are destroyed by an exposure to moist heat at 45° C. of 30 minutes' duration.

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Pathogenicity for lower animals.—Not found pathogenic for rabbits (intra-venous and intra-peritoneal inoculation), for guinea-pigs (subcutaneous and intra-peritoneal inoculation), or for tame mice (subcutaneous and intra-peritoneal inoculation).

18. **Streptothrix beta** (C. Price Jones).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 48 hours or later, up to fourteen days, as a buff-coloured expansion, sinking into medium. Stab culture: a deep cup of liquefaction, and a series of superimposed discs along the track of the needle. There is slow but complete liquefaction, and an amber coloration of the medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 24 hours as buff-coloured, more or less isolated, firmly implanted discs; the surface at first smooth, later becoming raised and limpet-like, and covered with chalky efflorescence. Later there is a brown pigmentation of the medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 24 hours. The medium is slowly liquefied and darkened.

On *potato* at 37° *C.*—Growth uncertain; subcultures frequently failing; appears within 48 hours; a raised, wrinkled, yellow buff-coloured growth, giving a gritty sensation when touched with the platinum wire; later covered by white chalky efflorescence. There is no pigmentation or erosion of the medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as discrete, white, fluffy colonies at bottom of tube. Faint brown coloration of medium in old cultures.

In *alkaline litmus milk at* 37° *C.*—After three days the medium has pinkened; by eighth day the colour is discharged and a granular deposit has settled to the bottom, leaving a clear brown alkaline liquid.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 50° C. for 30 minutes, but are killed by an exposure to 55° C. for the same period.

Pathogenicity for lower animals.—Not pathogenic for rabbits or for guinea-pigs.

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19. **Streptothrix nigra** (Rossi-Doria).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 48 hours as small flattened discs, sinking into medium; surface covered with white chalky efflorescence, and surrounded by narrow dark brown zone of pigmentation. (This pigmentation is not so deep as in the case of *Streptothrix nigrescens.*) Stab culture: a series of superimposed round fluffy colonies along the track of the needle. By tenth day the liquefied gelatine is pigmented to one third of its depth (cf. *Streptothrix nigrescens*). There is complete liquefaction of the medium ultimately.

On *maltose-peptone agar at* 37° *C.* and 22° *C.*—Appears after 48 hours; greyish-white discs with polished waxy surface; later covered by white chalky efflorescence. The discs are surrounded by zones of commencing brown pigmented medium. Growth and pigment production are more active, and chalky efflorescence is produced more readily at 22° C. than at 37° C.

On *inspissated horse serum at* 37° *C. and* 22° *C.*—Growth appears within three days; more active at 22° C. than at 37° C. No liquefaction of medium; slight brown pigmentation of medium after seven days at 22° C., but not at 37° C.

On *potato at* 37° *C.* and 22° *C.*—Growth appears after 48 hours; slightly raised granular drab or buff-coloured growth, covered later by chalky efflorescence of a yellowish tint. There is a slight darkening of the medium, but no erosion.

In *peptone beef broth at* 37° *C.* and 22° *C.*—Growth appears within 48 hours as grey flocculent colonies at bottom of tube; later surface growth; deep brown pigmentation of broth, occurring earlier at 22° C. than at 37° C.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is pinkened; by eleventh day it has become a clear brown alkaline liquid.

Diastatic action.—Was manifested after three days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 60° C. for 30 minutes, but are killed by exposure to 75° C. for the same period.

Pathogenicity for lower animals.—Not pathogenic for rabbits and guinea-pigs (Rossi-Doria).

Note.—We have examined cultures received from Kral, of Prague, as *Streptothrix nigra, Streptothrix chromogenes,* and *Cladothrix*

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dichotoma (*Streptothrix nigrescens*), and have also examined cultures obtained from water of an organism which corresponds with the last of these. We find that the last *Streptothrix nigrescens* answers in the main to the descriptions of *Cladothrix dichotoma*, and that the cultures of *Streptothrix nigra* and *Streptothrix chromogenes* closely correspond with each other, the following differences being obtained in cultures :—*Streptothrix chromogenes*. (*a*) On nutrient maltose agar at 37° C. and 22° C., chalky efflorescence was never formed. (*b*) On potato, out of many trials, only two cultures were obtained, and these at 22° C.; it appeared after the fifth day, a brown, finely nodular growth, soon being covered by a thin white powdery efflorescence, and later there was a black-brown pigmentation and slight erosion of the medium. (*c*) In alkaline litmus milk at 37° C. there was no clearing of the medium till after a month, when the tube was removed to room temperature; the milk then became a clear brown alkaline liquid.

20. **Streptothrix nigrescens**, syn. *Cladothrix dichotoma*.

STAINING CHARACTERISTICS.—Cultures up to four months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 48 hours as small flattened greyish-white discs, sinking into medium and surrounded by faint brown zone of pigmentation. Stab culture: a series of superimposed fluffy round colonies along the track of the needle. The medium is completely liquefied by tenth day, and the liquefied gelatine is pigmented to half of its depth (cf. *St. nigra*).

On *maltose-peptone agar at* 37° *C. and* 22° *C.*—Growth appears after 48 hours as grey discs with polished waxy surface, later covered by white chalky efflorescence; there is dark brown pigmentation of medium growth; pigment production and chalky efflorescence are freer at 22° C. than at 37° C.

On *inspissated horse serum at* 37° *C. and* 22° *C.*—Growth appears within three days; more active growth at 37° C. than at 22° C.; there is no liquefaction of medium; a slight brown pigmentation of medium after seven days at 22° C., but not at 37° C.

On *potato at* 37° *C. and* 22° *C.*—Growth appears after 48 hours as a granular layer varying in colour from drab to chrome or orange-yellow; later (third day at 22° C.) it becomes covered with a dead white chalky efflorescence. There is deep brown pigmentation, but no erosion of the medium.

In *peptone beef broth at* 37° *C. and* 22° *C.*—Growth appears within 48 hours as whitish-grey flocculent colonies falling to bottom of tube;

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later surface growth occurs. The medium has a deep brown to black pigmentation.

In *alkaline litmus milk at* 37° *C. and* 22° *C.*—After three days the medium is pinkened; by eleventh day it has become a clear brown alkaline liquid, which later darkens to black.

Diastatic action.—Is manifested within seven days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 50° C. for 30 minutes, but are killed by exposure to 55° C. for the same period.

21. **Streptothrix odorifera** (Rullmann).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 24 hours as a whitish flocculent expansion sinking into the medium. Stab culture: a flocculent expansion at the top, submerged in liquefied gelatine, and a feathery outgrowth along the track of the needle. The medium is completely liquefied by tenth day; there is a light brown pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 72 hours as raised, drab-coloured, semi-translucent colonies with smooth varnished surface, which afterwards becomes reticulated; later there is a deep brown pigmentation of the medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after twelfth to eighteenth day; there is no liquefaction or pigmentation of the medium.

On *potato at* 37° *C.*—Growth uncertain, only one subculture obtained out of eight tubes inoculated; appears about tenth day as a finely granular growth of light brown to grey colour; slight, white efflorescence; light brown pigmentation, but no erosion of medium.

In *peptone beef broth at* 37° *C.*—Growth appears about tenth day and is very scanty, but in an old (two to three months) culture that had been standing at room temperature the amount of growth was considerable; a grey, loose, flocculent deposit at bottom of the tube; no surface growth even in old cultures; there is brown pigmentation of medium.

In *alkaline litmus milk at* 37° *C.*—Growth occurs; after four weeks there is faint pinking of the milk, but no clearing.

Diastatic action.—Was manifested after seven days' incubation in starch peptone broth at 37° C.

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Resistance to heat.—Cultures are killed by exposure to 45° C. for 30 minutes.

22. **Streptothrix graminarium** (Berestnew).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Aërobe; very slight growth under anaërobic conditions.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 72 hours as white, chalky, confluent discs, with faint pink shade, depressing medium. Stab culture: a series of superimposed, grey, flattened discs along the track, and a chalky surface expansion submerged in a layer of liquefied gelatine. There is slow but complete liquefaction; no pigmentation of the medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 48 hours as round colonies, flat at periphery, with raised dome-like centre, of an even chalky surface, white with faint pink tinge; later there is a brown tinting of the medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 24 hours, and resembles the growth on agar; no liquefaction or pigmentation of medium.

On *potato at* 37° *C.*—Growth appears after 48 hours, and resembles that on agar, the colonies being rather more heaped up. There is a light brown diffuse pigmentation, but no erosion of the medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as greyish-white "powder-puff" colonies at bottom of tube; no pigmentation of broth.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is pinkened; after a month it has become a clear brown alkaline liquid, which afterwards assumes a deep brown or black colour.

Diastatic action.—None manifested after fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures are killed by an exposure to 45° C. for 30 minutes.

23. **Streptothrix Gabritschewskii** (Berestnew).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 72 hours as a bright, rusty red to chocolate-coloured warty mass sinking

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into the medium. The surface soon becomes dusted with a fine white efflorescence. Stab culture: a series of minute, discrete, globular colonies along the track of the needle; above they are faintly coloured like the surface growth, but at lower end of the track they are almost white. There is slow but complete liquefaction of the medium, which has a brownish-red pigmentation ("tawny port").

On *maltose-peptone agar at* 37° *C.*—Growth appears after 48 hours as a raised, chocolate-red, warty mass, with finely rugose surface, powdered with delicate white efflorescence; there is deep red-brown pigmentation of the medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 48 hours. There is no liquefaction of the medium.

On *potato at* 37° *C.*—Growth appears after 48 hours as a raised, reddish-brown, finely granular layer, covered later by a fine white powdery efflorescence. There is a chocolate pigmentation, but no erosion of the medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 72 hours as a fine yellow sandy layer, later feathery, flocculent colonies at bottom of the tube; a fine powdery surface growth. There is a dark amber to brown pigmentation of the medium.

In *alkaline litmus milk at* 37° *C.*—Growth occurs, but the reaction and appearance of the medium are not obviously altered after twenty days' incubation.

Diastatic action.—None manifested during fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist exposure to 45° C. for 30 minutes, but are killed by exposure to 60° C. for same period.

24. **Streptothrix melanotica** (C. Price Jones).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Obligatory aërobe.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 48 hours as a buff-coloured mass sinking into medium. Stab culture: a surface expansion resting at bottom of a deep cup, but very slight growth along track after one month. The gelatine is softened, but no active liquefaction occurs. There is no pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 24 hours as slightly raised, firmly planted buff-coloured discs, later becoming more raised and wrinkled, and covered by a chalky efflorescence, which latter appears by reflected light of a greyish colour, but black by

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transmitted light. Later there is a faint brown tinting of the medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 24 hours; there is no liquefaction or pigmentation of the medium.

On *potato at* 37° *C.*—Growth appears within 48 hours as a buff-coloured raised nodular layer, soon becoming covered with a grey chalky efflorescence (the growth beneath being black); the medium is blackened and much eroded.

In *peptone beef broth at* 37° *C.*—Growth appears after 24 hours as discrete white fluffy colonies at bottom of tube; surface growth in old cultures. There is no pigmentation of the medium.

In *alkaline litmus milk at* 37° *C.*—After three days the medium is pinkened, and by eighth day has become a clear brown acid liquid.

Diastatic action manifested after three days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 60° C. for 30 minutes, but are killed by exposure to 65° C. for same period.

Pathogenicity for lower animals.—Not pathogenic for rabbits or guinea-pigs.

Note.—This organism was isolated twice from broth cultures inoculated with a deposit obtained from filtered sound rum, but when rum was inoculated from spore cultures no growth occurred, and subcultures and plates made at varying periods were sterile. This organism was, therefore, probably an air contamination.

25. **Streptothrix pluricolor** (Terni).

STAINING CHARACTERISTICS.—Cultures up to three months old, stained by the Ziehl-Neelsen method, show no acid-fast portions.

CULTURAL CHARACTERISTICS.—Aërobe; very slight growth under anaërobic conditions.

On *gelatine at* 22° *C.*—Streak culture: growth appears after 72 hours; a greyish-white powdery chalk layer, yellow on under surface. Stab culture: a chalky surface expansion, fine feathery growth along track, thicker and of faint brown colour at upper end; there is no liquefaction or pigmentation of medium.

On *maltose-peptone agar at* 37° *C.*—Growth appears after 48 hours; a spreading, powdery layer of a pink colour; there is a diffuse light brown pigmentation of medium.

On *inspissated horse serum at* 37° *C.*—Growth appears after 48 hours; there is no liquefaction or pigmentation of the medium.

On *potato at* 37° *C.*—Growth appears after 72 hours; a raised, granular mass of grey to rusty red colour, in part covered by fine

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white efflorescence; there is brown pigmentation, but no erosion of the medium.

In *peptone beef broth at* 37° *C.*—Growth appears after 48 hours as a powdery veil on the surface and a flocculent mass at the bottom of the tube; there is a faint brown pigmentation of the medium.

In *alkaline litmus milk at* 37° *C.*—Growth occurs, but reaction and appearance of the medium are not obviously altered after twenty days' incubation.

Diastatic action.—None manifested after fourteen days' incubation in starch peptone broth at 37° C.

Resistance to heat.—Sporulating cultures resist an exposure to 45° C. for 30 minutes, but are killed by an exposure to 60° C. for the same period.

APPENDIX III.

Various species and cultures of streptotrichese referred to in the paper, but not examined by the authors.

1. Streptothrix described by Aoyama and Miyamoto (*see* p. 81).

The organism stained by Gram's method, and by Gabbett's modification of the Ziehl-Neelsen method; the threads did not stain equally, portions of them remaining uncoloured. Under anaërobic conditions growth was very scanty, but Aoyama and Miyamoto did not consider their experiments on this point satisfactory, and were going to repeat them.

On *glycerine-agar* there were small, scarcely visible colonies of a whitish colour after twenty-four hours' incubation at 33° C.; in older cultures the colonies had a nodular appearance, and showed a dark opaque centre of a yellowish colour, and a thinner whitish margin. In stab cultures in glycerine-agar small white colonies are seen near the surface; deeper there is very little growth. On *blood-serum* growth appears after twenty-four hours in the form of yellowish surface colonies; growth is not vigorous on this medium. On *nutrient gelatine* growth is scanty. In *bouillon*, and in *urine-peptone-bouillon*, fine, greyish-white, chalky when on the surface colonies appear after two days' incubation; these cohere, and sink to the bottom as a flocculent deposit. This flocculent deposit itself never becomes yellow, but shows a "mother-of-pearl" sheen. In old cultures the broth assumes a brownish tinge. In *sterilised water* dust-like flocculi

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appear on the surface, afterwards sinking to the bottom; a similar growth appears in 5 *per cent. glucose solution in water.* On *potato*, at first small white colonies appear; these coalesce to form a single mass. After some days the under surface of the growth assumes a brownish-yellow tint, the upper surface at first remaining white, but afterwards becoming brownish also; growth on potato forms a loosely friable mass. Growth was also obtained on *carrot* and other vegetable media; such growth was usually at first whitish, then becoming yellow; sometimes it was yellow from the commencement.

Growth, usually scanty, was obtained on *raw fish* and on *oysters*. On moist *cotton tissue* no growth occurred. In *milk* there is first a yellowish surface growth, and later a yellowish crust forms at the side of the tube; the milk is not curdled.

Five guinea-pigs were inoculated, either with fresh pus or with subcultures of the streptothrix obtained from it. Guinea-pigs 1 and 2 received intra-peritoneal injections, and died on the sixth and eleventh days respectively. After death both showed a hæmorrhagic exudation into the peritoneal sac, with the formation of numerous grey nodules containing the streptothrix on the membrane. Guinea-pigs 3 and 4 received injections into the thoracic cavity and died on the twentieth and the fourth days after. The one which died on the fourth day showed an infiltration of the tissues at the point of inoculation, and a hæmorrhagic effusion into the pleural sacs; nodules were found on the surface of the pleural membrane, and in the kidneys, spleen, lungs, heart muscle, and left occipital lobe. The other of this pair of guinea-pigs showed a hæmorrhagic exudation into the pleural sac, with numerous fibrinous adhesions; there were also nodules on the pulmonary and diaphragmatic pleuræ, on the epicardium, and in the lungs close to the pleural surface. The fifth guinea-pig, inoculated into the jugular vein, died in five days. After death both pleural membranes were seen to be slightly inflamed, but there was no exudate; both lungs were hyperæmic, and contained numerous nodules, each about the size of a millet seed. The heart muscle was infiltrated with similar small nodules. The animal happened to be a pregnant doe, and cultures of the streptothrix were obtained from the heart blood, and from the blood of the placenta.

Other inoculation experiments on rabbits, white mice, and hens gave no obvious result.

Note.—From the very full and clear account which Aoyama and Miyamoto give of the organism which they isolated, it seems highly probable that they were in reality dealing with *Streptothrix Eppingeri*.

2. Streptothrix described by Berestnew in Cases 1 and 2 (*see* p. 78).

The organisms isolated from these two cases were considered as pro-

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bably belonging to the same species, although there were slight differences. The streptothrix from Case 1 grew better anaërobically than it did aërobically; the organism from Case 2 showed equal growth under either condition. The organism stained by Gram's method. It died out after three generations of subculture. Cultures were obtained on agar, glycerine-agar, glucose-agar, and blood-serum. Growth commenced after incubation at 36° C. to 38° C. for 48 hours, and appeared as whitish, opaque, rather brittle, nodular colonies, which grew into the depth of the medium. The organism was not pathogenic for rabbits, guinea-pigs, or tame mice.

3. Streptothrix described by Berestnew in Case 3 (*see* p. 78).

This organism grew better aërobically than anaërobically. It stained by Gram's method. The best growth was obtained in broth, and then on the following media, in the order given: glycerine-agar, gelatine-agar, agar with human blood-serum. In *broth* growth appeared as white, opaque, dust-like masses, which collected at the bottom of the tube; numerous small colonies also attached themselves to the side of the tube. On *agar*, by the third day, there was a growth of small, isolated, sharply contoured, spherical, finely granular, greyish-white colonies, with moist shining surface. These attained their maximum size—about that of a poppy-seed—after four days' incubation; later the surface became rougher and uneven, and the colonies appeared of a deep yellow colour by transmitted light. On *potato* there was no obvious growth; after five to seven days' incubation a faint glaze could be seen over the surface inoculated, in contrast with the unbroken free surface elsewhere. On *gelatine*, incubated at 22° C., there was a scarcely perceptible, very slow growth; the gelatine was not liquefied. In *milk* growth occurred, and the medium began to clear after an incubation of from three to four weeks. The inoculation of rabbits and guinea-pigs subcutaneously resulted in an infiltration at the point of injection, which slowly disappeared. Intra-peritoneal inoculation of other animals of the same species produced no obvious effect.

4. Organism, probably a streptothrix, described by Berestnew as *Bacillus pseudo-actinomycosis* (*see* p. 81).

The organism did not grow in the presence of oxygen, but cultures on agar and in broth, to which equal parts of hydrocele fluid had been added, showed growth after two days' incubation at 37° C., under anaërobic conditions. On *agar*, there were small white granular colonies, which were the size of a pin's head after five days' incubation. In *broth* the growth appeared as an abundant white flocculent deposit. These cultures had an unpleasant penetrating odour, reminding one of that of a culture of *Bacillus tetani*.

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Dogs, rabbits, and guinea-pigs were inoculated subcutaneously into the pleural sac and into the peritoneal sac with cultures four days old on agar, but without any positive results; in tame mice intra-peritoneal inoculation was followed by a localised purulent peritonitis, with an appearance of "cachexia" after two weeks.

The cultures died out after three weeks on artificial media.

5. Streptothrix described by Hayo Bruns (*see* p. 80).

Did not stain well with ordinary aniline dyes, nor by the Ziehl-Neelsen method; stained best by Gram's method.

Growth obtained only under aërobic conditions; optimum temperature 35° C. to 38° C., no growth below temperature of 25° C.

On *gelatine*, growth occurred after about four weeks' incubation at 24° C. to 26° C., and after eight weeks was still very scanty; there was no softening or liquefaction of the medium. On *agar* and on *glycerine-agar* growth was apparent after six days' incubation; it was of a yellowish colour, spread over the surface, and was firmly implanted in the medium. In *broth*, growth appeared as broken-up yellowish flocculi at the bottom of the tube; there was never any surface growth. Growth on *blood-serum* and on *potato* was less vigorous than on the preceding media.

No positive results were obtained after subcutaneous, intra-venous, and intra-peritoneal inoculation of rabbits, guinea-pigs, and mice.

6. Streptothrix described by Garten (*Cladothrix liquefaciens II, see* p. 76).

Isolated from pus on plates of gelatine with blood-serum incubated at 16° C. to 18° C.; growth appeared as small greyish-white points. On the sixth day the colonies were the size of a pin's head, and firmly implanted in the medium; gelatine began to liquefy on the third day, liquefaction was complete on the eighth. Growth on *potato* was more active at 37° C. than at 22° C. At first the colour of the growth was much the same as that on the potato, later a thin white efflorescence appeared on the surface, and later still the medium became discoloured. On *agar* there was an abundant growth after 24 hours' incubation at 37° C. The growth at first is of grey-white colour, with a shining surface which is much wrinkled. The growth penetrates some distance into the medium, which in time becomes darkened; about the fourth day a chalky efflorescence appears, which by the twelfth day has completely covered the medium. On *glycerine-agar* growth is less vigorous, and there was no efflorescence, even after ten months. In *broth* and in fluid *blood-serum* growth appears as greyish-white flocculi, which mostly collect at the bottom of the tube; any surface growth shows a chalky efflorescence. These fluid media, exactly neutralised, developed a slight acid reaction after three or four days'

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incubation. On solid blood-serum, good growth occurs within twenty-four hours; the serum is completely liquefied by the sixth day, a clear fluid resulting.

The pathogenicity of the organism was tested on twenty-four rabbits, ten guinea-pigs, and three pigeons, positive results being obtained with two rabbits and one guinea-pig. One rabbit which received an intra-peritoneal inoculation was killed on the eighteenth day; there was a small tumour the size of a pea on the serous coat of the bowel, and from this the streptothrix was recovered in culture. The second rabbit also received an intra-peritoneal inoculation, and was killed after four weeks; a swelling about the size of a bean was found at the point of inoculation; there were several smaller nodules close to this, and others which varied in size from that of a pin's head to that of a pea were found in the mesentery and in the serous coat of the colon. From these lesions the streptothrix was isolated in culture.

The guinea-pig was killed during the fifth week after inoculation. At the point of inoculation on the parietal peritoneum there was a small nodule from which a culture of the streptothrix was obtained.

7. Streptothrix described by Hesse (*see* p. 76).

Stains by Gram's method. Is an obligatory aërobe; young cultures have no true special smell; old cultures develop a mouldy odour, reminiscent of Camembert cheese.

On *gelatine* there is a good growth by the third day; liquefaction commences on the fourth or fifth, and is complete within a week. After seven to eight months the liquefied gelatine became of a darker colour, and showed a reddish tint. On *ox serum* the growth is of a yellow colour, the colonies being about the size of a lentil after five days' incubation at 37° C., and a snow-white efflorescence appears on the surface. The serum is liquefied, and for some time after there is no change in its colour, but in old cultures (after six months) the liquid assumes a reddish-yellow tint. On *agar* growth resembles that obtained on blood-serum. On *glycerine-agar* growth was vigorous, and the under surface assumed a dark yellow colour, which was not seen on plain nutrient agar. In *broth*, by the end of 48 hours, there were fine pin-point flocculi to be seen; within a week these flocculi had increased to the size of a pin's head, but did not grow beyond that. These flocculi had the appearance of a nucleus with a more delicate periphery. The colonies collect at the bottom of the tube; the broth remains clear, and retains its alkaline reaction. On *potato* small yellow granules appear after two days' incubation; the growth spreads over the surface of the medium, and a white efflorescence develops on it.

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Rabbits, guinea-pigs, and white mice were inoculated subcutaneously, intra-venously, and intra-peritoneally, but without any positive result in any case.

8. Streptothrix described by Paul Krause (*see* p. 80).

Stains by Gram's method, and is not acid-fast when stained by the Ziehl-Neelsen method. Optimum temperature 37° C., no growth obtained at 22° C.; growth better under aërobic than under anaërobic conditions. No production of acid, alkali, sulphuretted hydrogen or other gas, or of indol was observed.

On *glycerine-agar* growth occurred after four days' incubation; the colonies were isolated, deeply implanted in the medium, and showed irregularly toothed margins; the cultures were scanty, and growth feeble. In *broth* coherent spherical colonies formed at the bottom of tube; there was no surface growth. On egg albumen and on glucose-agar, and in 1 per cent. peptone solution, litmus milk, ascitic fluid, and sheep serum, growth was obtained, but showed nothing characteristic. On potato, glycerinated potato, gelatine, and in sterilised water no growth was observed.

Subcutaneous and intra-peritoneal inoculation of rabbits, guinea-pigs, and mice gave no obvious result.

9. Streptothrix described by Norris and Larkin (*see* p. 80).

The organism was first grown on slices of fresh kidney from rabbit; from this it was transplanted to bouillon, and then to solid media. It stains by Gram's method, and is not acid-fast when stained by the Ziehl-Neelsen method. Optimum temperature 37° C., growth obtained at as low a temperature as 24° C.; grew in broth equally under aërobic and anaërobic conditions. No special smell. On neutral or slightly acid *glycerine-agar* colonies were visible after 48 hours' incubation at 37° C.; the colonies attained their maximum growth in a few days, measuring then from 3 to 4 mm. in diameter; growth extends into the substance of the medium. In *agar* stab cultures isolated discoid colonies were obtained along the track of the needle. In *broth* growth occurred in the form of small, white, hard, discoid colonies, which adhered to the side of the tube, or as larger flocculent masses at the bottom of the tube. In litmus glucose-broth there was no obvious formation of gas, but the colour was slowly changed to red; the broth is subsequently decolourised.

In *litmus milk* the colour soon becomes markedly red; clotting occurs between the fourth and the seventh day, the clot is "soft, finely divided, and occupies the whole of the fluid." No growth was obtained in peptone solution, or on plain or glycerinated potato.

The pathogenicity was tested on seventeen rabbits and three guinea-pigs; "the streptothrix is pathogenic to rabbits and guinea-pigs,

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but death rarely supervenes from its action. In the rabbit subcutaneous injections and the escape of broth cultures into the peritracheal tissues, and intra-peritoneal injections in rabbits and guinea-pigs, produce local death of tissue and abscesses encapsulated by extensive zones of granulation tissue."

10. Pathogenic streptothrix described by Rullmann (*see* p. 59).

Stains by Gram's method. Is a facultative anaërobe, optimum temperature 37° C.; growth obtained on ordinary media.

Pathogenic action was tested on seventeen rabbits, seven guinea-pigs, a horse, and twelve mice, and a positive result was obtained in the majority of the experiments. From some of the animals a streptothrix was isolated, which Rullmann thought resembled his *Streptothrix odorifera* (*see* Appendix I, No. 21), but it is not quite clear to us whether he considered the two organisms as being identical.

11. Streptothrix described by Scheele and Petruschky (*see* p. 81).

In the sputum the organism stained by Gabbett's modification of the Ziehl-Neelsen method.

On *agar* a growth of pure white colonies, firmly implanted in the medium, was obtained; these cultures had a characteristic smell. Growth was also obtained on *gelatine* and in *broth*. No growth obtained on potato or on glucose-agar.

12. *Streptothrix lacertæ*, described by Terni as *Actinomyces lacertæ* (*see* p. 70).

Found in greyish nodules in liver of lizards.

A yellowish growth was obtained on glycerine-agar.

Various reptiles (*Lacerta viridis*, *L. agilis*, *L. murialis*, and *Coluber viridiflavus*) were inoculated with cultures, and greyish nodules in the liver were produced.

13. Organism described by Acosta and Grande Rossi as *Cladothrix invulnerabilis*, non-pathogenic (*see* p. 66).

Isolated from water; grows equally well under aërobic and anaërobic conditions. Was not destroyed by six successive exposures to a temperature of 100° C.; the development of cultures heated to 120° C. was retarded for several days.

On *agar* growth appears after 48 hours' incubation; is deeply implanted in medium; at first of a whitish colour, afterwards becomes yellowish. On *gelatine*, growth white; slow liquefaction of the medium. In *broth* small flocculent colonies develop. On *potato* there is a free whitish growth, which becomes covered with chalky layer; these cultures have a strong mouldy smell, and the medium darkens in colour. In *milk* a yellowish layer forms on the surface, and the milk clears from above downwards. In *sterilised water* good growth occurs.

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14. Streptothrix described by Kedzior as a thermophilic cladothrix (*see* p. 67).

Isolated from sewage and from water of river Spree.

Facultative anaërobe; optimum temperature 55° C.; growth at 45° C. is slower than at 55° C.; at 35° C. growth only appears after two or three days' incubation, no growth at or below 30° C.; growth was obtained at 60° C., but not at 70° C. Formation of spores was not observed at the lower temperature limit (35° C.). Cultures have an aromatic odour, resembling that of carpenters' glue.

On *agar* growth occurs after 16 hours' incubation at 55° C.; surface colonies have a well-defined spherical outline, and are deeply implanted in the medium; a white, chalky efflorescence, arranged in concentric rings, develops on the surface.

In *broth* growth was obvious after 36 hours' incubation at 60° C., and appeared in the form of flocculi. A firm surface growth, covered with chalky efflorescence, is soon formed. This surface growth becomes "brittle," and the snow-white efflorescence assumes a dirty green appearance.

The addition of glucose or glycerine to the agar or broth appears to have no influence on the rate of growth.

The most favourable medium for sporulation is potato.

The vitality of spores is not affected by the action of 5 per cent. carbolic acid solution during ten days. The spores also retained their vitality after five weeks' desiccation, and after exposure to direct sunlight for 8 hours.

The spores are not destroyed by exposure to steam at 100° C. for 4 hours; cultures not containing spores are killed by exposure to the same temperature for a few minutes.

15. Organism described by Dor (*see* p. 79).

Isolated from pus which contained yellow granules consisting of filaments "as long as a leptothrix," which did not stain by Gram's method. The pus was not collected under aseptic conditions, and was possibly contaminated. No growth had occurred on *gelatine* after twenty days.

In *broth* a deposit of very fine "pellicles" formed at the bottom of the tube; the medium itself became cloudy, and after twenty days emitted a fœtid smell. The organism grew rapidly on blood-serum, and badly on the other media tried.

16. Organism described by Sawtschenko (*see* p. 79).

Isolated from a case which clinically resembled an actinomycosis. In the pus there were granules, described as being very like those of an actinomycosis, but which appeared to consist of zooglœal masses of bacilli.

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The organism was an obligatory anaërobe; optimum temperature about that of the body. The organism grew well in blood-serum, in glycerine broth, and on glycerine-agar. The broth became clouded, and liquid blood-serum was coagulated without the formation of any acid. The forms described as "very short bacilli" did not stain by Gram's method. On exposure to oxygen these forms developed into long, unbranched threads.

Note.—It is just possible that in the case of the organisms described by Dor and Sawtschenko, the cultures worked with were not absolutely pure.

APPENDIX IV.

Some additional species of streptotricheæ.

1. *Streptothrix albido-flava.* Described by E. D. Rossi-Doria, "Su di alcune Specie di Streptothrix trovate nell' aria," 'Annali dell' Instituto d' Igiene sperimentale della Università di Roma,' p. 399, 1891.

Obtained from air twice out of forty-nine examinations.

Growth on *gelatine* appears after 36 to 48 hours' incubation at 20° C. By the third day the colonies appear as compact masses of a yellow tint, with a rather lighter margin. After the tenth to twelfth day the colonies have an appearance as if dusted over with magnesia. The appearance is due to the development of aërial spore-producing hyphæ, which are considerably thicker than the deeper filaments. Liquefaction of the medium commences on the twentieth to twenty-fifth day, progresses slowly, and in old cultures is complete.

On *agar* growth tends to spread over surface. There is a peripheral zone, smooth, sometimes translucent, and with wavy outline, and a central rough, heaped-up portion of a yellow colour. The formation of spore filaments is rare, and occurs only in the peripheral zone, which then appears as if dusty on the surface.

On *potato* growth rather slow; resembles that on agar. Sporing filaments are rarely produced. The potato does not become pigmented, and the yellowish pellicle—in parts transparent, in parts appearing powdery—distinguishes this species from others.

In *milk* there is a luxuriant yellow surface growth. The milk, without any preliminary coagulation, becomes perfectly transparent, of a straw-yellow colour, and acid reaction.

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Subcutaneous, intra-peritoneal, and intra-venous inoculations produced no obvious results in the case of four rabbits and five guinea-pigs.

2. *Streptothrix carnea.* Described by Rossi-Doria, *loc. cit. supra.* Obtained from air once in forty-nine examinations.

Growth on *gelatine:* colonies appear as minute points after four to five days' incubation. The surface is covered with aërial spore-producing hyphæ, and appears as if hidden by minute spheres of a whitish-pink colour. In stab culture in gelatine, the nodules which form along the tract of the needle are smaller than those of other species isolated by Rossi-Doria from the air. The gelatine is not liquefied.

On *agar* growth appears in the form of very small globular colonies which present a variegated appearance. Portions of colonies not covered by sporing filaments appear of a flesh colour, those portions bearing sporing filaments being of a delicate whitish rose colour.

On *potato* the colonies resemble those on agar; they are small and of granular appearance.

In *milk* luxuriant growth by from eighth to tenth day. There is a surface growth of a flesh colour, the cream layer being of an orange to canary-yellow tint. The medium is not altered in appearance after three months' growth, and its reaction is slightly alkaline. Pathogenicity was tested by intra-peritoneal or intra-venous inoculation of a rabbit and two guinea-pigs; no obvious result obtained.

3. *Streptothrix aurantiaca.* Described by Rossi-Doria, *loc. cit. supra.*

Obtained from the air once in forty-nine examinations.

Growth on *gelatine* appears in form of circular colonies, which look like drops of wax. On successive days the growth becomes yellow, then orange-yellow, and finally of a deep orange colour. Later the surface has a powdery appearance. The medium is not liquefied.

On *agar* colonies are circular and raised, of a yellow to orange colour, sometimes resembling those of *Streptothrix albido-flava.* Later the colonies coalesce, and form a mammillated pellicle covering the whole surface. After fifteen to twenty days a colony is of a deep yellow or almost red colour at the centre, and of a paler tint at the periphery. The surface of the growth is never covered with sporing filaments.

On *potato* there is good growth, the colonies become confluent, and are of a yellow to orange colour. Sporing filaments are not formed.

In *milk* grows slowly; after about twenty days a surface crust of an orange colour forms. The milk is not altered in appearance, and after three months' growth its reaction is slightly alkaline.

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This organism shows no growth under anaërobic conditions.

Its pathogenicity was tested on two rabbits and two guinea-pigs; the result was negative.

4. *Streptothrix rubra.* Described by Ruiz Casabó, "Descripción de un Cladothrix cromógeno," 'Chronica medicó-quirurgica de la Habana,' 1894; ref. 'Centralblatt für Bakt.,' Bd. xvii, 1895.

Obtained from sputum. Growth on *gelatine* appears after 24 hours; by the fifth day the gelatine is liquefied half through, and liquefaction is complete after a month. A pellicle of white growth floats on the surface of the liquefied gelatine.

On alkaline *peptone-agar* a bright red growth was obtained. A similar growth was obtained on glycerine-agar. In stab culture in agar growth occurred after 50 hours, but viewed by transmitted light showed no coloration.

In *broth* growth first occurs at the surface; the red colonies afterwards fall to the bottom.

On *potato* growth first occurs within 24 hours, and is of a red colour by the second day.

Growth occurs in *milk.*

Inoculations performed on guinea-pigs produced no obvious result.

5. Streptothrix described by Thiry as *Cladothrix mordoré*, "*Bacilles et Cladothrix polychromes,*" 'Archives de Physiologie,' 1897, p. 283.

Obtained from an anginal exudate.

Growth on *gelatine* is active, and forms a greyish-yellow pellicle, afterwards covered by an efflorescence, on the surface of the medium, which is quickly liquefied.

On *agar:* growth on this medium is characteristic. The colonies are isolated, raised, and of a grey to slightly violet colour; later they are covered with a white efflorescence, and surrounded by a zone of reddish-brown pigmentation, which has a metallic reflection. This "auréole mordoré" is due to the formation of pigmented lamellar crystals. Growth occurs on *blood-serum*, which is quickly liquefied.

On *potato* the growth quickly spreads over the surface of the medium, and is covered by a greyish efflorescence. The medium becomes of a blackish-brown colour, and its surface shows a metallic reflection.

All cultures have a strong mouldy smell.

The organism is not pathogenic for the guinea-pig.

6. Streptothrix isolated from a horse, described by G. Dean, "A New Pathogenic Streptothrix," 'Transactions of the Pathological Society of London,' vol. li, 1900.

Obtained from an abscess which formed near the angle of the mandible.

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Stains by Gram's method; not acid-fast when stained by Ziehl-Neelsen method.

Grows best under aërobic conditions; optimum temperature 35° C. to 38° C.

No growth obtained on potato, gelatine, blood-serum, milk, or egg albumen.

On *agar* growth appeared on the third to fifth day as small, opaque, isolated white colonies. These grew slowly, and after three weeks presented the appearance of small masses of white coral.

In *broth* a whitish coherent mass of growth forms at bottom of tube. The organism was pathogenic for the rabbit, guinea-pig, and pigeon; the result of inoculating mice was doubtful.

7. *Streptothrix Hoffmanni.* Described by Gruber as *Micromyces Hoffmanni.* "Ueber eine neue Eiterung erregende Microbeinart, *Micromyces Hoffmanni*," 'Transactions of the Seventh International Congress of Hygiene and Demography, London,' 1891, vol. ii, p. 65; ref. 'Centralblatt für Bakt.,' Bd. x, 1891.

Isolated from the air.

Stains by Gram's method. Is a facultative anaërobe. Grows best at 37° C.

No growth obtained on nutrient gelatine or potato; very scanty growth on inspissated blood-serum; good growth on agar and in bouillon.

Subcutaneous injection in one dog, in mice, and in pigeons gave no result.

Subcutaneous injection of rabbits resulted in the formation of a local abscess.

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10. *Localisation in the motor cerebral cortex of the anthropoid.*

By C. S. Sherrington, F.R.S., and A. S. F. Grünbaum.

The subject of cerebral localisation is one of obviously great extent, and we should be lacking in all sense of proportion did we attempt before such a meeting as this to deal with it except in regard to some portions with which as experimentalists we are acquainted at first hand.

We may recall, however, how very different is the point of view from which the cerebral cortex is to-day regarded from

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that taken prior to the observations of Hughlings Jackson and the experiments of Hitzig and of Ferrier. Up to that epoch, experimentalists had failed to get evidence of localisation of function in the cortex of the hemispheres, though in microscopic structure the great sheet of grey matter presented such similarity to nervous formations regarded elsewhere as nerve centres. Progress of knowledge in regard to the nervous system has been always indissolubly linked with determination of localisation of function in it. This has been so from the time of the Bell-Magendie discovery of the differentiation of function in the two spinal roots; and another instance is Flourens' delimitation of the respiratory centre in the bulb. The discovery of localisation of function in parts of the cortex laid the foundation for an advance of knowledge regarding it which has led to the supply to the student of charts of its functional topography very similar to the geographical maps of continents which are supplied to the schoolboy. And just as the schoolboy, looking over the political map of a continent, is liable to forget the complexity of the populations and states which it so simply represents, so we, looking at the brain chart of the text-book, are liable sometimes to forget the unspeakable complexity of the reactions thus rudely symbolised and spatially indicated.

If we may be allowed an *a priori* consideration it is this,—that though it is not surprising that such territorial subdivision of function should exist in the cerebral cortex, it is surprising that by our relatively imperfect artifices for stimulation we should be able to obtain clear evidence of the localisation which does exist. The nerve-cell chains that together build up the nervous system are in the architecture of that system so arranged that the longest of them all tend to pass through the cerebral cortex. Every increase in the number of links composing a nerve-cell chain seems to increase greatly the uncertainty of its reactions under artificial excitation. With increase in number of links goes increase in numbers of side branches and connections. The difficulty of getting long cell-chains to react in a regular way under artificial stimulation seems greatly enhanced by the multiplication of the side connections, because the momentary condition of any cell-chain is in part a function of the condition at the moment of all the other cell-chains with which it is connected. The cortex cerebri might therefore

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well have been expected to yield under artificial stimulation only extraordinarily irregular results. We owe to Hitzig and to Ferrier the pregnant demonstration that as regards the motor region this expectation is not well founded. It is mainly of the reactions of the Rolandic area of the cortex that we shall venture to speak. Ferrier showed that the application of faradic currents to that cortex excites with great regularity movements which vary in distribution as the electrodes are moved from place to place in the region, but that the reactions remain very regularly similar under repeated application of the stimulus to any one and the same spot. Ferrier's mode of indicating the topographical arrangement of the reactions he obtained is seen in his well-known diagrams of the cortex. His motor centres, as he termed them, were marked in his figures by circular areas. "The areas have no exact line of demarcation from each other, and where they adjoin stimulation is apt to produce conjointly the effect peculiar to each."[1] He showed these motor centres to extend forward over the frontal lobe, including there reactions of the eyeballs. Regarding their extension round the upper edge of the hemisphere and down upon the mesial surface he noted them in the marginal convolution. "This convolution in the parieto-frontal region gave rise to movements of the head and limbs apparently similar to those already obtained by stimulation of the corresponding regions on the external surface."[2]

This ever-memorable original research by Ferrier ranks among the classics of experimental neurology and physiology. It has been followed by a number of kindred contributions from workers largely of our own country—names familiar to us all,—Schäfer, Beevor, Horsley, Mott, Ballance, and others. These have led to the detailed knowledge we possess of the localisation of functions in the cerebral cortex of the common ape, the macaque. These are concisely given in the well-known figures of the text-books. It was an interesting step further when Dr. Beevor and Mr. Horsley published eleven years ago their observations on the localisation of the motor functions in the Rolandic cortex of an orang-outang. Their

[1] 'Functions of the Brain,' London, 1876.

[2] Ibid.

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experiment has remained the single one for which an anthropoid species of ape has been laid under contribution. It has exercised a notable influence on the scheme of motor localisation adopted as probably obtaining in the brain of man. An experiment upon the brain of an anthropoid ape presents special interest from two points of view—(1) the cortical organ in these species is, except for man, at its highest development; and (2) it presumably presents that type of development which culminates in man.

Of the three or four species of anthropoid apes that are known, most authorities agree that the gorilla is that which possesses the most highly developed cerebrum; next to it probably comes that of the chimpanzee, and last, but not far below that of the chimpanzee, comes that of *Simia satyrus*, the orang-outang. But there are great individual differences, and the simpler examples of chimpanzee brains seem inferior in development to well-developed examples of the brain of the orang.

We have recently had the opportunity of making physiological experiments on all the known species of anthropoid apes. As it is upon the chimpanzee that we have obtained the larger number of our observations, we will mention first our results upon that type. We have used, besides the ordinary chimpanzee (*Troglodytes niger*), the rare variety of which the celebrated "Sally" of the "Zoo" was a specimen, *Troglodytes calvus*, by some considered a separate species.

In the chimpanzee the scheme of topography which we find existent is illustrated by the accompanying figure. We invite attention to the extent of the so-called motor area presented by it. The extent and arrangement differs considerably from that found by other observers in the lower apes and from that found in the orang by Dr. Beevor and Mr. Horsley.

The so-called motor area occupies unbrokenly the whole length of the precentral convolution, and in most places the greater part or the whole of its width. It extends into the depth of the Rolandic fissure, occupying the anterior wall, and in some places the floor, and in some extending even into the deeper part of the posterior wall of the fissure. We have examined nineteen hemispheres, but have never found the motor area extend to the free face of the post-central convolution.

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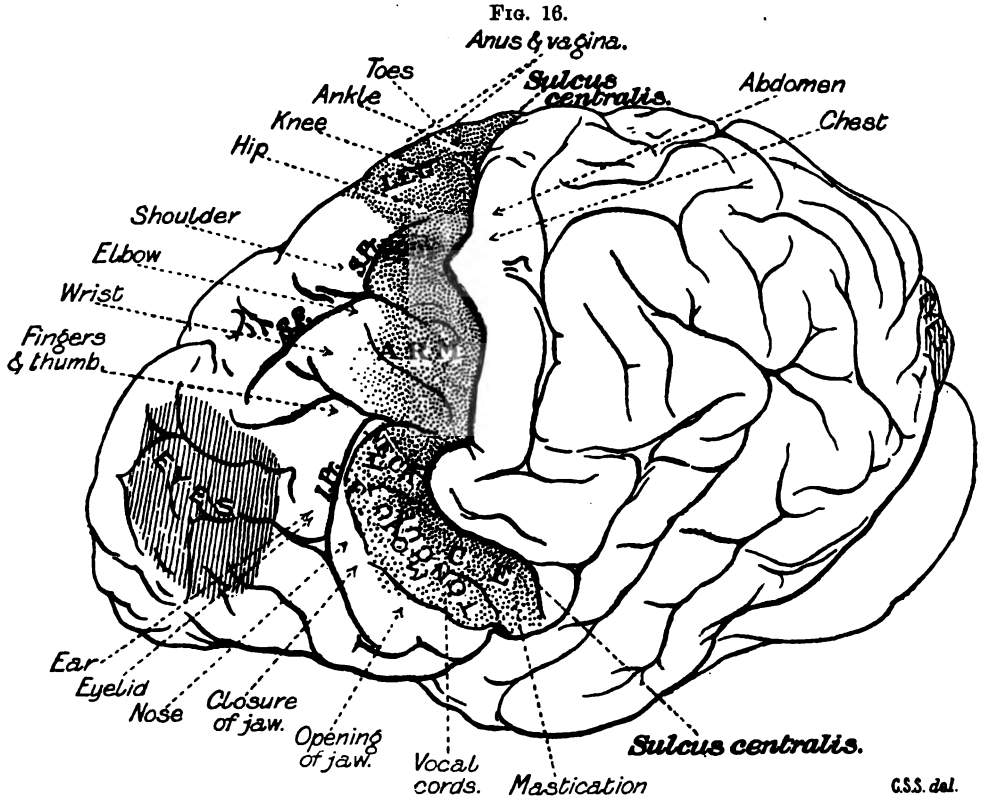
At the upper mesial edge of the hemisphere the motor area extends round and down upon the mesial face of the hemisphere; but we have not found it reach the calloso-marginal fissure. The anterior limit of the motor region is, in great part, not coincident with any fissure. The front portion of the region usually dips into and across the upper part of the

FIG. 16.



The left hemisphere of brain of chimpanzee, showing the motor areas of the cortex.

superior precentral fissure, and lower down it not infrequently dips into the inferior precentral fissure. Occasionally the front edge of the region dips into almost the whole length of the superior precentral sulcus. It is not the extent of the motor area which appears to be variable, the variant is the sulcus itself. The great variety of individual pattern exhibited

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by the convolutions and sulci in these richly convoluted brains gives opportunity for studying critically the claim of value of these fissures as landmarks to the topography of the functional centres of the cortex. From this point of view their use for strict localisation is almost *nil*. Not only are the extremes of pattern exhibited by the convolutions extraordinarily different one from another, but the frequency of the individual variation is so great that hardly a pair can be found in which the existent convolutions are, when compared with the same minuteness as we apply to the functional centres, really closely alike. Professor Schäfer, in his important contribution to the physiology of the motor cortex in 1887,[1] pointed out that the fissures of the cortex do not mark in any sense the boundaries of the functional areas of the organ. Our examination of the considerable number of anthropoid brains we have now worked through convinces us that not only do the fissures of the frontal region not mark physiological boundaries, but that they are not reliable even as landmarks to the functional topography, since their relation is too inconstant. The degree of subjection of these fissures to individual variation and the frequency of their asymmetry in the two hemispheres stands in striking contrast to the far greater constancy from individual to individual and far greater symmetry of bilateral situation, which we have found hold good for the arrangement of functional centres of the motor region as examined by physiological methods. A practical outcome of this is that we have found it essential for accurately detailed localisation, when we have desired the opening through the skull to be kept to a small size, not to trust to the anatomical details of the exposed cerebral surface, but to obtain orientation as to the topography by application of the electrodes and observation of the movement, if any, which was excited. In our early experiments we thought to obtain much help by having at hand an individual brain already experimented upon; and we thought to save time in recording the results of the fresh experiment upon chart outlines prepared from the specimen already worked upon. But the variation of the convolutions from individual to individual has been too great to allow of these expedients being employed. Defeated in this way, the only recourse must be to

[1] 'Festschrift zu Karl Ludwig,' 1887, Leipzig.

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the electrodes. Two landmarks of real value are the genua of the Rolandic fissure.

A matter of some surprise to us has been the ease with which faradism elicits movements from this so-called motor region of the cortex of the anthropoid. It is a general belief that for excitation of the cortex in man the intensity of the faradic currents has to be much greater than that effective for the cortex of the monkey. Our predecessors with the orang-outang state that the cortex of that animal required much more intense electric stimuli than the cortex of the bonnet monkey. Their impression was, however, based on no direct comparison. We have actually compared the excitability of the cortex of the anthropoid with that of the bonnet monkey by employing exactly the same current in each case. We find that the excitability as measured by the least intensity of current required to evoke motor reaction is practically the same in the anthropoid and in the lower ape. The motor cortex of the anthropoid, though undoubtedly far more complex in many ways than that of the lower ape, remains as readily amenable to electric stimulation. If, therefore, it is really necessary to employ intense faradisation for the human motor region, that is a difference between the human motor region and that, not only of the lower ape, but of the anthropoid.

A further point cognate to the above on which our experience differs from that of our predecessors regards epileptiform discharge from the cortex. It will be remembered that Dr. Beevor and Mr. Horsley never observed epilepsy to follow excitation in the brain of their orang, although their electrodes were occasionally kept in contact for five seconds. Though we also find that in some individual anthropoids the tendency for the discharge from the cortex to take an epileptiform character is very slight, yet in other individuals the tendency under apparently the same external conditions is strong. In the majority of the individuals upon which we have experimented, cortical epilepsy has been easily provoked.

Turning to the localisation in the cortex, the sequence of representation starting from below upward follows closely that already known for the lower apes. Broadly speaking, the sequence runs—tongue, mouth, nose, ear, eyelids, neck, hand, wrist, elbow, shoulder, chest, abdomen, hip, knee, ankle, toes,

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perinæal muscles, anus, and vagina. It is noticeable that movements of the eyeballs do not appear in this list. As did Beevor and Horsley in the orang, so we in the chimpanzee find a frontal area extending into the middle aud inferior frontal convolutions, excitation of which gives conjugate deviation of the eyeballs to the opposite side. We find this area separated from the area yielding the other movements by an intervening space of so-called "inexcitable" cortex, as our predecessors found in the orang. We find this intervening space broken, however, by a small area whence movements of the eyeballs can be elicited, which partially bridges between it and the upper facial region on the precentral convolution.

The sequence of representation of movement which we note follows a plan more in accordance with the order of the spinal series of segments than that hitherto obtained, because we find between the representation of shoulder and hip an area which, next to the shoulder, yields unilateral movement of the chest muscles, and, next to the hip, yields unilateral movement of the abdominal muscles.

A noteworthy discrepancy between our results and those of our predecessors is regarding the extension of the excitable motor region to the free surface of the post-central convolution. We have seen nothing to lead us to include that surface or any part of it in the motor area of any of the anthropoids we have used. In our experience the electrodes, carrying even very strong currents, when placed upon the surface of the post-central convolution, fail to evoke any obvious effect, though when placed, using a weaker current, upon the precentral they evoke extremely wide-spread movement. We may add also that though small lesions in the precentral convolution cause marked paralyses and descending spinal degenerations, similar and larger lesions in the post-central do not produce even temporary paralysis nor any unequivocal degeneration.

With regard to the degenerations, it is noteworthy that from a hand-area lesion the spinal pyramidal degeneration shows in the chimpanzee the feature of a ventral direct pyramidal tract not obviously inferior in size to that of a man. On the other hand, a lesion somewhat smaller, situate in the region for the ankle and foot, produced a pyramidal degeneration in which a direct ventral tract is not obvious. The hand-area lesion gave a

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heavy degeneration of the homolateral pyramidal tract in the lateral column on the same side as the cerebal lesion.

As regards the symptoms resulting from the cortical lesions, the extirpation of a great part if not of the whole of the hand-area from the right hemisphere caused an immediate severe crossed brachioplegia without the slightest sign of paresis in either face or leg. The paresis affected most the fingers, which were kept helplessly semi-extended, the wrist being dropped. The elbow seemed little, if at all, affected, but the shoulder seemed distinctly paretic, there being difficulty in raising or abducting the upper arm. The paresis diminished quite rapidly, and in six weeks' time the animal had largely recovered the normal usefulness of the limb.

A lesion in the leg-area similarly caused temporary paresis of the opposite leg, especially in the toes and at the ankle-joint. The lesion was smaller and the recovery more rapid than with the arm-area lesion. It is perhaps noteworthy that the knee-jerk, which showed no alteration under the arm-area lesion, here showed exaltation immediately, that is, a quarter of an hour after the leg-area lesion, and that when the paresis to inspection had passed off, the knee-jerk still exhibited great briskness on the crossed side.

Although we have used a more minutely localised method of excitation than our predecessors, we have not found in any of our anthropoids those remarkable inexcitable intervals noted by them between the main regional divisions of the area,—that is, between the upper and lower facial areas, between the facial and the arm, between the arm and leg.

On the other hand, we have seen often confirmed what our predecessors with the orang have well pointed out, namely, the greater integration of localised representation of movements in the anthropoid as compared with the lower ape. Thus there is only one of the fingers that we have not seen move separately and alone under excitation of certain points of the cortex; again, isolated movement of the pinna of the ear, of the tip of the tongue, rare in the lower monkeys, are easily obtainable in the anthropoid.

Finally, one word with regard to the extent of the so-called motor area. From our observations we think it probable that perhaps as much of that area lies hidden from the surface in

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the sulci as actually lies at the free surface on the convolutions. Nevertheless, we endorse the opinion expressed by Beevor and Horsley that the so-called motor area in the anthropoid brain forms altogether a smaller fraction of the total surface than is found in the lower types of monkey. If it has grown in extent —as undoubtedly it seems to have done,—other regions belonging to that so-called inexcitable field whence electric stimulation excites no obvious response have increased still more. It is especially with the exploration of that great inexcitable field that the progress of research has to deal. We cannot help thinking that this progress will have to look for means to the patient combination of clinical and microscopical research rather than to the excitation experiments of the laboratory.

We would call attention to the fact that the results on the gorilla confirm those we have obtained on the chimpanzee and orang. This is a matter of interest, since many considerations go to show that the gorilla's is the highest form of brain excepting only that of man himself.

We have ventured to submit only the broadest features of the results at present obtained by us. The detailed collation of our observations may bring out points of interest of a more special kind, but the process of collation will be a matter of considerable time. *December* 17*th*, 1901.

11. *On a case in which cyanosis and plethora occurred in association with adherent pericardium.*

By J. Lorrain Smith and H. L. McKisack.

The following case presented changes in the blood similar to those which have been described in certain cases of cyanosis from valvular heart disease. The number of red corpuscles per c.mm. was increased to over six millions, and the hæmoglobin was over 100 per cent. The heart lesion in this case was adherent pericardium, and this had in a secondary way interfered with the cardiac function. The case furnished, therefore, an excellent opportunity for the application of the carbonic oxide

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method in the study of the exact conditions as regards the volume of the blood and the total amount of hæmoglobin in the circulation in a case of plethora of this type.

The clinical history of the case was the following:

Patient, M. B—, a boy aged 12, was admitted to the Royal Victoria Hospital, Belfast, on November 17th, 1900. The family to which he belonged consisted of eight members, of whom one had died of consumption, the other seven being healthy. The boy's medical history was that in 1898 he had influenza. In 1899 (November) he had suffered from a swelling in his right knee. This disappeared under treatment by bandaging. In May, 1900, he had typhoid fever. In September, 1900, he noticed a "swelling" on the right side of the abdomen in the hypochondrium. This caused him no pain, and attracted his attention only by its size. Subsequently he noticed he was out of breath after exertion, and that he could not run as far as other boys.

State on admission (November 15th).—He had the appearance of a fairly developed and fairly nourished boy. He weighed, without clothes, 64 lbs., or 3 lbs. less than the average. His skin and the mucous membrane of his lips had a bluish tinge, which suggested a venous condition of his blood. He had a slight cough. His appetite was good, and his tongue was clean.

The abdominal swelling complained of was found to consist in an enlargement of the liver. The lower edge of this organ could be easily felt reaching three inches below the costal margin. The upper margin of the liver dulness reached the fifth rib in the nipple line, and the seventh interspace in the axillary line. The superficial veins over the abdomen were distended, and the abdominal wall was somewhat tense. The percussion note, however, was tympanitic, and there was no sign of ascitic fluid.

The spleen was enlarged, the anterior border of the dulness being about one inch beyond the normal line. Mensuration of the body at the level of the tip of the eighth costal cartilage showed that the right segment was larger than the left by about one inch.

Thorax.—The area of cardiac dulness was slightly increased. The cardiac impulse was neither visible nor palpable. There was no retraction of intercostal spaces in the precordial area.

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The apex-beat, as it could be ascertained by auscultation, was found displaced outwards to just beyond the nipple line. There were no murmurs.

The rate of the pulse was increased to 110—120 per minute. The tension was somewhat decreased.

Lungs.—At the time of admission a few sonoro-sibilant rhonchi distributed generally over the lungs were heard, but these with the accompanying cough disappeared in a few days. The lungs were otherwise normal. Temperature was normal.

The synovitis of the right knee had completely disappeared; the movements of the joint were perfectly natural. There was a slight enlargement of the internal condyle. There was no œdema of either leg. The urine was free from albumen. It was acid, and had a specific gravity of 1010. The average quantity was about 22 oz. per diem. The urea (average of a few observations) was 1·5 per cent. There was no bile in the urine.

History of the case in hospital.—The patient soon after he came into hospital, though confined to bed, began to develop ascites. The evidence of this condition was quite distinct by the middle of December. By this time he had gained 11 lbs. in weight. In the following month, *i. e.* up till the middle of January, he gained only 2 lbs. This gain in weight could, as we will later show, be altogether accounted for by the accumulation of fluid in the serous cavities.

The blood was systematically examined during the two months, and great interest attaches to the conditions revealed.

The total quantity of hæmoglobin and total volume of blood in the body were estimated by the carbonic oxide method. (The details of this method are fully described in a paper by Haldane and Lorrain Smith, 'Journal of Physiology,' vol. xxv, p. 331.) At the same time the absolute and differential enumeration of the corpuscles was carried out.

Date.	Vol. of CO.	Saturation of hæmoglobin.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin.	Volume of blood in c.c.	Red corpuscles per c.mm. in millions.	White corpuscles per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. body-weight.	C.c. of oxygen per 100 grms. body-weight.
1900. Nov. 29	43·0	8%	537	114%	2557	6·34	9·00	29	8·8	1·85

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As regards the first observation, on November 29th, it is to be remarked that the amount of CO administered was too small to give reliable results. The administration of carbon monoxide is perfectly harmless in the majority of cases, but difficulties may be experienced with patients suffering from weakness of the heart, and in these cases it is necessary to proceed very carefully at the first examination of the blood. This observation is introduced because it is closely confirmed by the subsequent examinations, when much larger quantities of carbon monoxide were administered.

The outstanding facts revealed in this examination are these:— The hæmoglobin per c.mm. is 114 per cent.; the red corpuscles 126 per cent. of the normal. The increase in corpuscles is therefore greater than that of the hæmoglobin. This condition of the blood is the one which is found in chlorosis. In that form of anæmia the individual red corpuscle is poorer in hæmoglobin than the normal. It is interesting to observe that in the blood in plethora a similar condition prevails to a moderate extent.

The total quantity of hæmoglobin in the circulation is found to be more than twice as great as the normal. The method employed here directly estimates the total capacity of the blood for carbon monoxide, and therefore also for oxygen. The measure of this capacity is translated into a measure of the hæmoglobin. In the normal individual, the measure of the capacity of the blood to carry oxygen, in relation to the body-weight, is found to be ·83 c.c. per 100 grms. In this case the ratio is 1·85 c.c., and from this we conclude that the blood contains more than double the normal amount of hæmoglobin.

Our knowledge of the total amount of hæmoglobin enables us to estimate the volume of the blood in circulation. The further observation required is the ascertaining, by use of the hæmoglobinometer, how much of this total is present in a measured quantity of blood. The normal individual has a volume of 4·6 c.c. of blood per 100 grms. body-weight. This patient had in his circulation 8·8 c.c. The volume of the blood, therefore, was nearly doubled. The white corpuscles were 9000 per c.mm. The increase in volume in the plasma of the blood has not caused a diminution of the number of blood-corpuscles. The red corpuscles were, as we have seen, 6 millions per c.mm.

It is interesting to compare the blood of this case with the

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blood from a case of chlorosis where the anæmia is altogether due to dilution of the blood by excessive plasma. In chlorosis, on the average, the numbers of leucocytes per c.mm. are somewhat lower than in this case. Here dilution by plasma has less effect than in chlorosis (*v.* 'Transactions' of this Society, vol. li, p. 314). Another point on which comparison with chlorosis suggests itself is the following differential enumeration:

Polymorphonuclear	58·4 per cent.	
Small lymphocytes	31·6 „	} 40·6 per cent.
Large lymphocytes	7·6 „	
Transitional leucocytes	1·4 „	
Eosinophile cells	1 „	

The typical blood picture of chlorosis is seen in the following example:

Patient M. D—. Hæmoglobin, 48·6 per cent.; red corpuscles, 61 per cent.; white corpuscles, 6·30 per c.mm.

Polymorphonuclear	54 per cent.	
Small lymphocytes	35 „	} 44 per cent.
Large lymphocytes	9 „	
Eosinophile cells	2 „	

This comparison brings out another point of similarity between the blood in chlorosis and in this case of plethora, viz. the marked increase in the proportion of lymphocytes. Ehrlich has introduced the doctrine that the presence of an excessive proportion of lymphocytes is a passive phenomenon, due to an increased flow of lymph into the blood. In this case, as in a typical case of chlorosis, there is an increased volume of plasma in the circulation. We may therefore discover in these facts a certain amount of support of Ehrlich's doctrine. That in this case no factor is at work except that of an increase in the flow of lymph seems doubtful. In comparing this with subsequent observations the reasons for doubting the simple application of Ehrlich's principle will become apparent. In the meantime we may remind ourselves of the essential points of the argument as it is seen in its application by Houston to post-typhoid anæmia. In his paper ('British Medical Journal,' June, 1901) on this subject he shows that, in the first place, the number of lymphocytes per c.mm. is constant throughout the disease. The decrease in polymorphonuclear cells is in direct proportion to the decrease in the percentage of hæmoglobin. He concludes,

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therefore, that post-typhoid anæmia consists in a dilution of the blood by plasma containing a constant number of lymphocytes per c.mm. We will see later in how far this argument can be applied to the case under consideration.

Date.	Vol. of CO.	Saturation of hæmoglobin.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin.	Volume of blood in c.c.	Red corpuscles per c.mm. in millions.	White corpuscles per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. body-weight.	C.c. of oxygen per 100 grms. body-weight.
1900. Dec. 11	70·1	% 11·7	557	% 89	3355	6·02	7·30	29 + (4·5-14 fluid)	11·5	1·92

The volume of CO gas administered on this occasion (December 11th) was considerably increased. It is, however, still hardly sufficient to saturate the hæmoglobin to the degree required (15 to 20 per cent.) for a perfectly satisfactory observation.

It is to be noted that the total oxygen capacity of the blood is practically the same as at the time of the former observation. There is a sharp fall in the amount of hæmoglobin per c.mm., from 114 per cent. to 89 per cent. of the normal. There is a fall in the number of red corpuscles per c.mm. This, however, is less than the fall in hæmoglobin. A fall in the percentage of hæmoglobin, while the total amount remains constant, can mean only an increase in the plasma, and the calculation of the total volume here shows that nearly a litre of fluid has been added to the circulation.

The weight of the patient has increased 4½ kilos. in this interval, but we may regard this as an increase in the amount of fluid in the circulation and serous spaces of the body. The evidence of ascites became clear clinically, and the confirmation of this view regarding the increased weight was obtained at the *post-mortem* examination. We may therefore regard the weight of the patient as constant, viz. 29 kilos., for the calculation of the relation of the oxygen capacity of the blood to tissue in the body. When this calculation is completed the ratio comes out as 1·92 c.c. per 100 grammes body-weight. The volume of the blood is two and a half times the normal, or 11·5 c.c. in place of 4·6 c.c. per 100 grammes body-weight.

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There has been added to the body-weight 4½ kilos. The greater part of 1 kilo. consists of fluid added to the circulation, and the remainder is in the peritoneal and other serous spaces of the body.

The observations on the corpuscles at this date give the following results—

Red corpuscles 6 millions; leucocytes 7300 per c.mm. The differential enumeration was—

Polymorphonuclear	65·6 per cent.		
Small lymphocytes	30·2	„	33·4 per cent.
Large lymphocytes	2·4	„	
Transitional cells	·8	„	
Eosinophile cells	1	„	

The lymphocytes at this stage form about 33 per cent. of the whole, and this is to be compared with the former result, when they were found to amount to 40 per cent. There is relatively an increase in the number of polymorphonuclear cells, and even when we calculate out the absolute number of lymphocytes in the circulation, it is evident that the fluid which has been added to the circulation is poorer in lymphocytes than the blood into which it has been poured. In fact, if we take into account the reduction in the number of leucocytes and of the proportion of lymphocytes, we find that the fluid has not increased the total number of lymphocytes at all. It is clear, therefore, that in studying the passive addition of fluid to the circulation we must take into account factors which determine the presence or absence of a simultaneous increase of lymphocytes. In other words, the increase in lymphocytes seen to accompany dilution of the blood in post-typhoid anæmia does not occur with the form of dilution seen in this case.

Date.	Vol. of CO.	Saturation of hæmoglobin.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin.	Volume of blood in c.c.	Red corpuscles per c.mm. in millions.	White corpuscles per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. body-weight.	C.c. of oxygen per 100 grms. body-weight.
1900.		%		%						
Dec. 18	95	16·5	564	98	3100	—	—	29 + (5 fluid)	10·7	1·94

In the third observation, December 18th, the number of corpuscles was not observed.

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One or two points regarding the volume of the blood are to be noted. The percentage of hæmoglobin is again raised: the volume of the blood has diminished somewhat, to 3·1 litres from 3·3; the patient has increased in weight by about ·5 kilo. The accumulation of the fluid is therefore now taking place much more slowly than occurred in the interval between the first two observations. At the same time the circulation is emptying itself of the excessive plasma, which found its way into the vessels during the period when the serous cavities were filling more rapidly. The volume of CO gas given for this observation is more than double that of the first occasion. The total oxygen capacity is 564 c.c.

Date.	Vol. of CO.	Saturation of hæmoglobin.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin.	Volume of blood in c.c.	Red corpuscles per c.mm. in millions.	White corpuscles per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. body-weight.	C.c. of oxygen per 100 grms. body-weight.
1901. Jan. 2	98	% 17	570	% 98	3131	7·22	12·0	29 + (5·454 fluid)	10·8	1·96

In regard to the fourth observation, January 2nd, 1901, there is little further to remark. The weight has increased again by about ·5 kilo.; the percentage of hæmoglobin is the same as in the former observation; the total oxygen capacity is again slightly increased; the slight increase in the accumulation of fluid has not been accompanied by an increase of plasma; the number of red corpuscles has risen considerably. This recalls the fact which is abundantly proved in the study of chlorosis by the carbonic oxide method, that the multiplication of red corpuscles is a change in the blood most readily brought about, and has no obvious relation to the increase or decrease in the total amount of hæmoglobin in the circulation.

The differential enumeration was the following:

Polymorphonuclear . . .	66·4 per cent.
Small lymphocytes . . .	26 „
Large lymphocytes . . .	5·2 „
Transitional cells	1·6 „
Eosinophile cells	·8 „

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This is practically the same as in observation No. 2. The similarity of the two, in spite of an appreciable reduction in the amount of plasma in the blood, is of interest in view of the reference to Ehrlich's teaching on lymphocytosis.

Date.	Vol. of CO.	Saturation of hæmoglobin.	Total oxygen capacity of blood in c.c.	Percentage of hæmoglobin.	Volume of blood in c.c.	Red corpuscles per c.mm. in millions.	White corpuscles per c.mm.	Body-weight in kilos.	C.c. of blood per 100 grms. body-weight.	C.c. of oxygen per 100 grms. body-weight.
1901.		%		%						
Jan. 15	103·8	17·5	581	103	3026	6·94	8·20	29 + (5·909 fluid)	10·2	20·0

In the last observation the same general conditions of the blood are revealed. The total oxygen capacity has again slightly increased; there is a further slight reduction in the amount of plasma; the percentage of hæmoglobin per c.mm. has again increased somewhat; the weight of the patient has increased slightly by the further accumulation of a small quantity of fluid; there is nothing to record as regards the corpuscles; the differential enumeration was identical, practically, with that of observation 4.

That we are right in ascribing the increase of weight to the accumulation of fluid is seen by the constancy of the results when we eliminate this change in weight from the calculation, and regard the weight, 29 kilos., obtained before ascites was observed as the true body-weight throughout.

The patient was slowly losing ground, and it was decided to draw off part of the fluid, and at the same time to examine the abdomen by an exploratory incision, as the ætiology of the condition was very obscure. He was placed on the operating table and methylene was carefully administered. He began to show signs of heart failure before anæsthesia had been established, and though the administration was stopped at once and restoratives applied, no recovery of consciousness took place.

Though the relatives removed the body from the hospital, they were persuaded to allow a *post-mortem* examination of the thorax and abdomen.

Post-mortem report.—The abdomen was somewhat prominent, but the distension was not excessive; the superficial veins were

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well marked; the peritoneal cavity contained 3½ litres of clear straw-coloured fluid; there was no peritonitis, old-standing or recent; there was no enlargement of the lymph-glands in the mesentery.

The stomach and intestines were normal in appearance; the liver was enlarged, projecting distinctly below the costal margin; the capsule was tense, and the external appearance was that of congestion. On section of the organ, the characteristic signs of fairly advanced venous congestion were seen. The epithelial acini were opaque and greyish white in appearance; there was, however, none of the yellow colour seen in the epithelial acini in cases of advanced venous congestion in adults. The congestion had, in areas, caused very advanced atrophy of the epithelial cells. The organ weighed 2 lbs. 10 oz., and was therefore considerably heavier than normal.

The gall-bladder contained a small quantity of dark green bile.

The spleen was enlarged, weighing 8 oz.; the pulp was moderately hard and firm. The Malpighian bodies were still defined in the manner characteristic of the spleen of the child.

The kidneys were congested, but there was no sign of inflammation; capsule not adherent.

Thorax.—In each pleural cavity there were about 500 c.c. of fluid similar to that in the abdomen; the lungs were crepitant; there was no œdema; the tissue was congested, but not excessively, and there were no hæmorrhages.

There were a few discrete tubercles of the size of miliary nodules in the right lung, especially at the apex. There was no other sign of tuberculosis. The glands at the root of the lung were slightly enlarged; the medium-sized bronchi were slightly congested.

Heart.—The pericardium was completely adherent to the heart, and felt exceedingly firm and tough; the valves were competent. On making a section through the walls of the right and left ventricles, it was found that the pericardium and epicardium were replaced by very thick layers of connective tissue of the toughness and consistency of a layer of hard leather. Between the two layers were bands of connecting fibrous tissue. Over the left ventricle this double layer of connective tissue measured three quarters of an inch in thickness. Over the right

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ventricle it was not so thick, but it was of the same toughness as that already described. The cavities of the heart, and especially that of the left ventricle, were small in size. Though there was perhaps less than the normal amount of muscle, there was no distinct defect. The muscular tissue was soft, but it had not the appearance of fatty degeneration to the naked eye. There were none of the gross changes of myocarditis, but the microscopic examination showed that there was a small but extensive overgrowth of connective tissue through the muscle. The layer of epicardial connective tissue showed typical structure of tubercular tissue.

The heart and adherent pericardium weighed 12 oz.

Review of the case.

This case affords an opportunity of studying the effect on the circulation of the failure of the heart to establish the compensatory hypertrophy frequently found as a result of adherent pericardium. The reason for this failure was the compressing effect of the thickened and adherent pericardium, which we have compared to hard leather to convey an impression of its extremely unyielding character. The compression of the pericardial sac would interfere with the action of the heart, and leave it unable to keep the blood circulating with sufficient rapidity. In this manner cyanosis became a marked clinical feature of the case.

The harmful effect, however, was not confined to functional interference. It is to be noted the patient was only twelve years of age, and his growth, as shown by his weight, was very little short of the normal standard. The heart, however, must necessarily have ceased to grow from lack of room in which to expand, and the boy had reached an age at which it had become clearly unequal to the task of keeping a sufficient supply of blood circulating. Hence there occurred development of ascites, although the boy was at rest in bed. The effect, in short, was similar to that in an adult, when from some cause the valves cease to be competent. The stagnation of the blood in the venous system caused, in the first place, the enlargement of the spleen and liver. Subsequently there occurred the development

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of ascites and hydrothorax. A somewhat misleading condition throughout the course of the disease was the way in which these changes in liver, etc., already described, continued so much more marked than the other signs of failure of the circulation. There was no œdema of the legs at any period.

Further grounds of comparison with a case of valvular disease are afforded in the study of the blood. It has been pointed out by various observers that in certain cases of mitral disease an apparent concentration of the blood takes place. The hæmoglobin and the number of the red corpuscles are beyond normal (von Limbeck). In this case there was slight concentration of the blood at the time of the first observation. There was subsequently dilution when ascites, etc., set in, and still later there was a second phase of slow concentration, during which time the percentage of hæmoglobin increased from 89 per cent. to 103 per cent. The tendency to concentration might at first sight seem to be an effort at compensation. In any given case, the work necessary to be done by the heart in supplying oxygenated blood to the tissues would be the less if with the same absolute respiratory capacity there were a smaller total volume of blood. This explanation, however, throws no light on the increase in the total amount of hæmoglobin to more than twice the normal quantity.

Hayem, in his recent work on the blood ('Leçons sur les Maladies de la Sang,' 1900, p. 662), takes up the subject in the study of a case of congenital heart disease. He concludes that the cause of the increase in red corpuscles in the blood of his patient to about seven millions per c.mm. is due to the condition of cyanosis, or rather to the mixture of venous and arterial blood, which takes place in the heart. In other words, it is the effort at compensation for some respiratory insufficiency in the blood.

In the case we have described there is no question of the mixing of venous and arterial blood, but there is cyanosis due to deficient circulation. This also involves a respiratory defect, and might be explained on the principle which Hayem applies to his case of morbus cæruleus.

Hayem refers to the observations on the increase of corpuscles and hæmoglobin in the blood of persons who travel to high altitudes, and this he describes as a defence by the organism

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against the effects of the lowered oxygen tension of the air breathed.

In the case we have described, not only is the number of corpuscles increased per c.mm., but the total volume of the blood and the total amount of hæmoglobin is enormously increased. The observations on this case tend to prove that there was a constant struggle to keep down the volume of the blood. It may be that the increase in hæmoglobin was in some way to compensate for the breakdown in the regulation of the volume of plasma by the circulation. At this stage of investigation it is impossible to come to any definite conclusion on this subject, but it may be well to adduce the points which might be considered in any explanation of the condition. We have clearly two possibilities: there is, in the first place, as we have seen, the theory of Hayem, that cyanosis in heart disease is the cause of the percentage (and possibly absolute) increase of corpuscles and hæmoglobin. In the case before us there was a demand for hypertrophy of the cardiac muscle, but this, from the mechanical hindrance of the sac, was impossible. To cover the respiratory insufficiency of the circulation there was concentration of the blood, and increase in the total amount of hæmoglobin and number of red corpuscles.

The second possibility is that the exchange of fluid was the process, the disturbance of which constituted the primary lesion. We have seen as a fact that the volume of plasma was more than double the normal. We have clear evidence of a tendency for the plasma to become gradually reduced, as if the circulation were attempting to rid itself of the excess. In spite of this, however, the amount is still very large. Let us suppose that in consequence of the weakening of the heart, the regulation of the fluid exchange had broken down, and the blood-vessels could not empty themselves of excess of plasma. Compensation in some form must be brought about. Compensatory hypertrophy to restore the circulation by increasing the power of the heart having failed, the only possibility remaining would be that of increase of the hæmoglobin of the blood. Since the heart could pump through the lungs only a small quantity of blood, the demand would arise to make the blood of a maximal respiratory capacity, and should the plasma increase, the hæmoglobin must increase with it to meet the respiratory

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requirements. On these lines we may therefore build up another explanation of the changes in the blood.

Confirmatory evidence of this latter view of the blood changes is obtained in the study of chlorosis. In the onset of this condition it is noticed by the hæmoglobinometer and hæmocytometer that the hæmoglobin decreases in the corpuscles before the number of corpuscles per c.mm. is diminished. This, however, as has been pointed out, signifies merely an increase in the plasma, compensation for which takes the form of a multiplication of red corpuscles. These being more numerous than before are each furnished with an amount of hæmoglobin smaller than normal. There is no compensation as regards hæmoglobin. In chlorosis, therefore, whatever may be the cause of it, the primary change in the blood is a breakdown in the regulation of its fluid exchange.

We have further pointed out that in a sense this boy's blood was chlorotic in type at the time of the first observation, both as regards red and white corpuscles.

If we are justified in regarding the blood changes in this case as similar to those of chlorosis in their origin, viz. as due to a disturbance of the fluid exchange in the circulation, we find a contrast in the two conditions in the fact that here there is compensation, not only in corpuscles, but also in hæmoglobin, whereas in chlorosis no compensation is seen in regard to hæmoglobin.

It is of interest to note that the hæmogenetic tissues had not yet lost their power of producing an abnormal amount of hæmoglobin. There is a steady slight increase in the amount of hæmoglobin throughout the six weeks period of observation. It rises from a total oxygen capacity of 537 c.c. to one of 581 c.c., that is about 30 c.c. per month. If we assume that this is a rough measure of the rate of increase in the past, it is easy to calculate how long the process had been in existence. The capacity of this boy's blood should have been not more than 240 c.c. He had therefore gained nearly 300 c.c. In other words, for about one year the abnormal increase in hæmoglobin had been at work. On turning to the clinical history, we find that a year before entering hospital he had complained of a swelling in his right knee. Accordingly it seems probable that at this time a slight tubercular infection had taken place,

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resulting in synovitis of the knee, slight tubercular infiltration of the lung, and in a chronic form of tubercular pericarditis. The development of this chronic form of tubercular pericarditis led to the unusually thick layer of tough fibrous tissue, and in its slowly progressive course it was accompanied by the extraordinary development of the blood which we have described.

We beg to express our thanks to Dr. Thomas Houston for his assistance in the investigation of the histological changes in the blood in this case. *December 17th*, 1901.

12. *A new centrifuge.*

By J. W. H. Eyre.

Dr. Eyre showed a new electrically driven centrifugal machine, in which he had retained all the important features of the hand-driven machine, previously described at the meeting of the British Medical Association at Cheltenham in July, 1901. The chief points of interest in connection with the present model were—

1. That the disc carrying the centrifugal tubes was not fastened to the driving shaft, but merely rested upon a conical block of india-rubber, with which the driving shaft was capped, and in consequence of this arrangement the disc was self-balancing.

2. That the continuity of the driving shaft was broken by a flexible coupling, which further rendered the disc self-centring, and which prevented the possibility of bending stress being transmitted to the motor spindle.

3. The disc was held motionless during the insertion or removal of the loaded tubes, by means of a three-armed metal support, which could be moved by a small lever handle or fly screw placed below the basin of the machine, and rising or falling as required in a screw socket.

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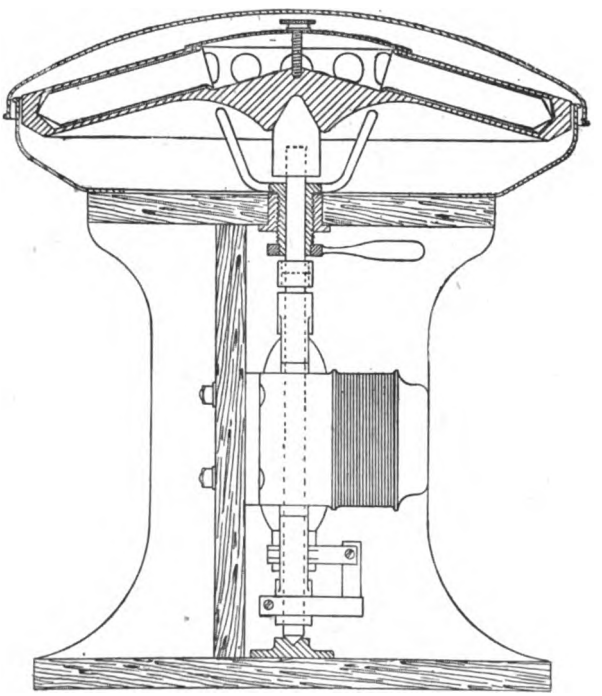
4. The motive power was derived from a small motor "coupled direct,"—that is, with the field magnets arranged around and embracing the vertical shaft; motion was therefore

Fig. 17.



communicated directly to the driving shaft, without the intervention of pulleys or wheels.

5. The motor was wound to produce 2500 revolutions per minute, which speed was transmitted to the disc without loss.

November 19th, 1901.

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13. *The occurrence in the pelvis of malignant tumours originating from adrenal remnants.*

By A. Eastwood.

[With Plate V.]

During embryonic life portions of suprarenal tissue are peculiarly liable to become detached from the suprarenal bodies and to settle elsewhere. They have been found after birth in the periadrenal fat, the liver, and the head of the pancreas, along the course of the suprarenal vein, in the solar plexus, and in the mesentery; they are of common occurrence in the substance and on the surface of the kidney, and not unfrequently they may be found descending towards the pelvis along the course of the spermatic or ovarian veins. Schmorl and others have found them in the spermatic cord; Friedland records a suprarenal "rest" situated between testis and epididymis; and Marchand, followed by many other observers, has collected numerous instances of their occurrence within the layers of the broad ligament.

Usually these bodies disappear, or at all events remain so small that they are only discovered accidentally in *post-mortem* examinations. Occasionally, however, they may, without assuming an active growth, yet become of clinical interest—when they occur, for example, in a situation where hernia is common. Thus Mr. Lockwood removed from the inguinal canal of a boy a small tumour which looked like a lipoma, but was shown by Andrewes to possess the typical characters of suprarenal tissue.

Except when they occur within or in close proximity to the kidney, it is very rare for these rests to develop into new growths. Marchand, however, has described an adenoma of an accessory adrenal, occurring in the broad ligament of a woman of 50, which measured 5 cm. by 3 by 3½. Still more interesting is the case recorded by Chiari of a man aged 44, with a highly malignant tumour of the suprarenal type, the size of a man's head, occupying the pelvis, and reaching above to the level of the lower border of the right kidney. The man died of recurrence after operation, and Chiari was able to demonstrate

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post mortem that the tumour was not traceable to kidney, suprarenal gland, or any other abdominal or pelvic organ. Apart from Chiari's case, which is well established, I have not been able to find a detailed and convincing record of a malignant suprarenal tumour occurring primarily in the pelvis. I must, however, briefly refer to two cases supposed to be of this character which have been described, the tumour in both cases involving the ovary. (1) Peham's case (of which I have only seen a very brief review, the original article not being accessible) is described as one of a cystic ovary, in the neighbourhood of which was a suprarenal rest which subsequently developed into a tumour and invaded the cyst wall. (2) Weiss's case of an unmarried girl of 17. The author's view is that the tumour originated in a suprarenal rest situated between the layers of the broad ligament, and in its subsequent growth extended into the hilum of the ovary. Ultimately it came to lie upon the fundus uteri, and contained the enlarged and partially infiltrated ovary as an excrescence upon its upper aspect. The tumour was characterised by its vascularity, consisting in many places of a network of capillaries surrounded by tumour-cells arranged concentrically several layers deep. It was hæmorrhagic, showed extensive fatty degeneration, and gave a glycogen reaction. In the broad ligament, quite independent of the tumour, was a rest containing normal suprarenal tissue. All these are highly interesting points, but hardly conclusive, because, although the features of Weiss's tumour have all been found in many suprarenal growths, they are not in themselves, even when taken collectively, exclusively characteristic of that class of growth. Weiss himself admits that the histological characters of his specimen are very different from those of the supposed parent organ, and his illustrations do not appear to me to be diagnostic of a suprarenal growth. I therefore cannot think that he has successfully excluded the possibility of his case being really an angiosarcoma commencing about the hilum of the ovary and subsequently invading the broad ligament.

I now propose to describe a malignant tumour closely connected with the uterus, and possessing characters which, I believe, point unmistakably to its origin from a suprarenal rest. Although Marchand and many subsequent observers have long ago suggested the strong probability that sooner or later a

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malignant broad ligament tumour would be found of the definitely suprarenal type, no case, so far as I know, has as yet been placed upon record both identical in situation and closely comparable in features with mine.

CASE 1.—Martha B—, aged 48, was admitted to Martha Ward of St. Bartholomew's Hospital on April 17th, 1900, under the care of Dr. Champneys; married ten years ago; never pregnant; catamenia always regular, not excessive, but painful; ceased at 40. Symptoms for fifteen months, severe during last nine months; pains over sacrum and hypogastrium and irregular losses, dark brown and sometimes offensive. Had noticed abdominal enlargement, and thought she was losing flesh. On examination Dr. Champneys found a solid tumour, moveable and dull to percussion, reaching midway to the navel. The uterus measured 2½ inches, was attached to the right, was not displaced, and was lying on the brim. Vaginal cervix healthy. On May 2nd Mr. Harrison Cripps performed abdominal section. The presenting part of the tumour was cystic, two pints of yellowish fluid having to be drained off before the solid mass of the tumour could be got out. The growth appeared to spring from the uterus, which was amputated through the top of the cervix, where the tissues appeared perfectly healthy. Both ovaries were removed at the same time and found to be natural. No other abnormalities noticed. The patient made a good recovery. On March 8th, 1901, she reported herself as being in perfect health, and allowed Dr. Champneys to examine her again. He found no evidence of recurrence and no other sign of disease. On December 9th, 1901, she again reported herself as quite well, and doing her work as usual.

The tumour, roughly oval, was, after hardening in formalin, bisected through its longest diameter and found to be mainly solid, though necrotic except at the periphery. The somewhat larger of the two fairly symmetrical halves contained the uterine tissue and the site of amputation. The smaller was, in other respects, similar in character. The cystic part was very necrotic, and showed under the microscope no lining membrane. The slightly larger half of the solid tumour measures in its longest diameter and in the plane of section 17½ cm., 11½ cm. at right angles to this diameter and in the same plane, and 5 cm.

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perpendicularly to the plane of section. The cut surface, yellowish in colour, shows numerous fibrous septa of a somewhat hyaline appearance, streaks of hæmorrhage, and some necrotic softening. The convex surface is somewhat nodular and covered with a tough, well-defined capsule, except in one or two places, where the nodules are uncovered. A slight cord-like thickening stretching across the capsule proved on microscopic examination to be the Fallopian tube. Sections taken from various parts containing the tube showed that, apart from being stretched out, it was normal in character, situated amid the outermost strands of the capsule, and unconnected with the growth. Situated somewhat laterally and embedded in the tumour is the remainder of the body of the uterus. A wedge-shaped piece has here been cut out to demonstrate more fully the anterior and lateral relations of this structure to the growth. Then a knife has been carried in an antero-posterior direction through the entire uterine substance and well into the tissue of the tumour on its posterior aspect. Naked eye inspection shows that everywhere the tumour substance is clearly separated from the uterus by a well-defined capsule. The outermost strands of the fibrous and muscular tissue of the uterus blend with the fibres of the capsule, but there is no evidence of transition between the tumour tissue internal to the capsule and the uterine tissue.

Microscopic examination.—(1) The uterine tissue presents no evidence of new growth. I have prepared sections from various parts at the plane of amputation, from the fundus, and from the entire length of intervening tissue. The mucosa of the fundus shows slight endometritis, such as is common at the climacteric; there is also some increase of the muscular and fibrous elements; there are no other abnormalities. The outermost and more fibrous elements of the uterus fuse with the outermost strands of the capsule.

(2) The capsule is composed mainly of fibrous tissue with some elastic fibres, and to a slight extent of unstriped muscle, and contains numerous blood- and lymph-channels. These channels are dilated and show sometimes a swollen endothelium, sometimes hypertrophy of their muscular walls. Some of them are engorged with blood-corpuscles, others contain a large amount of hyaline material with a few red corpuscles packed in a corner; others, again, contain the hyaline material alone.

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(3) *The substance of the tumour.*—The structure of the tumour consists of parenchymatous cells, which bear an intimate relation to fibrous tissue septa and to dilated blood- and lymph-channels. To a large extent the fibrous tissue passes inwards from the capsule, occasionally carrying with it a few fibres of unstriped muscle. It also appears to have originated in a certain degree from independent foci within the tumour, in immediate proximity to the vascular channels. The cells of the parenchyma, though differing widely in their size and outline, in the appearance of their protoplasm and the character of their nuclei, present everywhere stages of gradual transition between these diversities, and offer no indication of a mixed origin. Nor is there to be found any other appearance in the tumour which might suggest that we are dealing with a mixed growth. We have no sign of cartilage, for example, or of striated muscle, or of any other extraneous element; moreover, any appearance of a glandular, tubular, or cystic character which we do find is so obviously traceable to changes going on in the characteristic tissue of the tumour as to preclude the possibility of a foreign origin.

Let us now examine the histological characters in detail. Taking first an actively growing part close to the capsule, we find running inwards strands of fibrous tissue, broad at irregular intervals and intermediately very delicate. These septa are rich in capillaries, and sometimes appear to consist entirely of a flattened capillary tube. Between these delicate strands are cells arranged frequently in columns, often in double columns, sometimes in small circular islands. The cells are large, closely packed, with an irregular outline determined by the degree of compression, and obviously in a state of active proliferation. Their protoplasm is granular and vacuolated. Their nuclei are very large and stain well, possessing a rounded and sometimes a slightly oval contour, and often exhibiting in their centre a small, well-defined globule, staining only slightly, perfectly spherical, and somewhat glistening. They also have a tendency to vacuolation. Sometimes even quite close to the capsule the cells form larger groups, and show here and there a tendency to fuse together. When the protoplasm of a small group of cells thus unites it often leaves a clear, centrally placed lumen.

Next we may follow inwards one of the larger strands of fibrous tissue. It soon ramifies into a meshwork of trabeculæ

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of varying size and more or less delicate subdivisions. Within these trabeculæ are larger groups of cells, which very frequently assume a mosaic pattern. Their protoplasm is now clearer than before, their outlines well marked and polygonal, and their nuclei not generally so large, but rounded, centrally placed, often containing a nucleolus, and sometimes a glistening yellow globule.

Passing still further inwards, the same type of tissue is still the rule; but it rapidly becomes highly necrotic, until the brilliant red of the fibrous tissue, in specimens stained by van Gieson's method, is the only recognisable landmark. Penetrating such a region of general necrosis we occasionally find a narrow well-preserved tract, where the fibrous tissue marks off actively growing parenchymatous cells into very clearly defined alveoli. These alveoli often appear circular in section, containing a cluster of cells concentrically arranged. The middle of such a group often exhibits a lumen, which may be filled with fragments of nuclei and granular cell *débris* or may be quite empty. In some cases the lumen is large, and the surrounding cells consist of a well-defined single layer, thus presenting a very definitely tubular appearance.

There is, however, no definite rule as to the relative situation of these three types of structure. Both the alveolar type and the mosaic pattern type may occur in immediate relation to the capsule side by side with the arrangement in columns. All three show gradual stages of transition from one to the others.

Turning now to the blood-vessels, we find in many cases a fibrous proliferation of the outer coat, the tissue so formed running out into strands and trabeculæ which unite with those passing inwards from the capsule. Along these strands the tumour-cells arrange themselves in a uniform row, and fill up the intervening parts of the irregular network by grouping themselves into a mosaic pattern. In many places, however, we get a striking difference in the general appearance of a section, owing to the exudation from numerous dilated blood- and lymph-capillaries and the presence of patches of uniformly staining hyaline material, suggesting the colloid of the thyroid gland, both within the capillaries and in the adjacent tissue. The large tumour-cells show a marked tendency to group themselves round the endothelium of these channels, again creating an

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irregularly tubular appearance. In some places they border directly upon or even grow into the capillary lumen, but, owing to the more or less degenerative character of such parts, it is impossible to infer an original deficiency of endothelium.

The above features are the most important, not merely because I think they are strong evidence in favour of my diagnosis, but because I assume that in any tumour the character of the cells and their relations to the stroma and to the blood-vessels should be the primary considerations.

I now mention some interesting points of minor importance. A first glance at many sections, especially from parts on the road to degeneration, impresses me with the enormous size of many of the cells, their tendency to fall into plasmodia, and their huge deeply staining nuclei. As these appearances may be found in all kinds of malignant tumours and in artificially produced conditions, a description of them would lead me away from my subject. I therefore merely mention that this tumour exceptionally well illustrates various forms of cell degeneration, karyorhexis, pyknosis, cell-fusions, and cell-inclusions.

Hæmorrhages are frequent. Near to unaltered red blood-corpuscles, which have made their way into the tissues, are to be found patches of brown and yellow pigment, partly collected in the connective tissue, partly contained within the tumour-cells. The natural assumption, it seems to me, is that the cell pigment in these situations is not a special product of cell activity, but can be accounted for by the hæmorrhage.

Hyaline degeneration is noticeable in most of the connective tissue.

As regards fatty degeneration, I cannot lay much stress on my observations, since the material available for me had been kept for a long time in spirit, as well as in formalin. I find, by the Marchi method, that the fatty areas are very irregular and localised. Sometimes a small part of a section gives an intense black reaction, owing to the presence of fine globules within the cells and large globules external to them, whilst the rest of the section is unaffected.

In some sections, prepared and stained in the ordinary way, there are, after passing through xylol, spherical and oval extra-cellular globules, the nature of which I do not understand.

I have not had the opportunity of testing for glycogen.

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As regards the presence of pigment, which cannot definitely be associated with the absorption of altered hæmoglobin, I find, in sections taken from one or two peripheral parts of the tumour, that there are, in places not marked by vascular extravasation, groups of cells, several of which contain a centrally placed patch of brown pigment. In the centre of such a patch of pigment is sometimes seen a glistening yellow globule identical with the globules frequently seen in the cell nuclei. This pigment, although I should have felt confident in my diagnosis without it, is very interesting and highly suggestive of suprarenal origin, being quite unlike altered hæmoglobin.

I must now justify my diagnosis. I wish I could settle the matter outright by simply saying that, from my description, the tumour *is* like a suprarenal rest tumour and is *not* like anything else; but, owing to the extreme rarity of this type of growth in this situation, and the comparative frequency of other very puzzling tumours in the neighbourhood of the uterus and its appendages, I fear I must adopt the more labouring method of proof by exclusion.

Because the rest of the abdomen was found healthy at the time of the operation, and because the patient is still in perfect health nineteen months subsequently, the tumour removed was primary. The case is not therefore comparable to one described by Boissier and Cornil, and referred to by Ruge and Veit, of a carcinoma uteri, secondary to carcinoma of the suprarenal gland.

Both ovaries were removed and found healthy. The cervix, still within the woman's body, was also undoubtedly healthy. We may therefore exclude tumours from these two sources.

Now as to the uterine body. There are no signs of malignancy in the epithelium or glands of the mucosa. Very rarely it does happen that, prior to the commencement of carcinomatous degeneration, the uterine glands, still preserving their lumen, may penetrate the muscular coat and reach even to its serous aspect; then, becoming partially if not completely cut off from their communication with the uterine cavity, may, as a subsequent development, undergo carcinomatous degeneration; but it is practically impossible that any such rare occurrence ever did happen without leaving any trace behind it. Here there is not the slightest suspicion of such a process. It is therefore unnecessary to explain further that the characters of this tumour

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are not those of a carcinoma arising from uterine glands. For similar reasons a sarcoma or an endothelioma arising from the other constituents of the mucosa are out of the question.

I now come to the uterine wall, where we naturally think first of sarcomata. The microscopic characters at once exclude the commonest possibility, viz. that it might be a sarcomatous degeneration of a subserous fibroid. The only kinds of uterine sarcoma which will for a moment admit of microscopic comparison are those rare forms of angiosarcomata, described by Gessner and others, which undoubtedly arose from the perithelium of vessels in the uterine wall. The resemblance to the present case consists, of course, in the regions of dilated capillaries, where the tumour-cells are closely related to the vessel walls, and in the hyaline coagulated material in the neighbourhood; but angiosarcomata would quite fail to account for the characteristic columnar, mosaic, and alveolar dispositions and the characteristic types of cell found in the present case; and similar objections apply with still greater force to those very rare and imperfectly recorded uterine tumours which have been thought to be endotheliomata. Indeed, the really authenticated cases of endotheliomata uteri which I have been able to find do not offer the least resemblance, either in situation or in histological features, to the present case.

Of such eccentricities as the supposed development of carcinoma out of uterine muscle very little need be said. I have consulted the record of Liebmann's case of "myocarcinoma uteri," and my only comment is that in the present instance, at all events, the uterine muscle has not behaved in such an extraordinary fashion.

Hence I maintain that this tumour has not arisen from any of the normal or normally situated uterine constituents. But before definitely considering abnormal constituents I must briefly refer to that hotly debated class of tumours found occurring at the angle of junction between Fallopian tube and uterus. I cannot digress into a discussion of them; I can only express the view, which I believe is generally accepted, that, while many of these cases are congenital, some are simply primary carcinomata of the tube. The latter cannot be the true explanation here. Apart from the impossibility of an ordinary Fallopian tube developing a growth histologically comparable to the present,

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there is no evidence that in this case the tubes were in any way affected.

I now come to congenital tumours. Taking the simplest possibility first, it may be asked, Has this growth arisen from misplaced or intercepted uterine glands? I think it will suffice in answer, without entering into further reasons and refinements, to borrow an argument from Recklinghausen, which he employs for another purpose, to the effect that the uterine body is glandless until after birth, and that we could hardly suppose glands to become aberrant in later life.

Remains of the Wolffian body and duct give rise to many varieties of tumours in these regions. Much the most interesting is that peculiar class of new growths, so admirably described by Recklinghausen, which is often situated at the angle of junction of Fallopian tube and uterus. The situation of some of Recklinghausen's cases on the posterior, upper, and outer aspect of the uterine wall would correspond fairly well with the present case. But the microscopic characters are entirely different. Apart from the abundant presence of muscular fibres, the distinctive character of the tubes, with their single layer of columnar ciliated epithelium, their tendency to cystic dilatations, and the comb-like arrangement of the tubules into systems, makes up a picture which does not present the faintest resemblance to anything found in my sections. It is only necessary to add that other tumours recognised as springing from the Wolffian body (viz. the parovarian and those arising in the hilum of the ovary) and cysts originating from the duct of Gärtner require no consideration here.

Lastly, it is requisite to point out that the present specimen is not a "mixed" tumour; it contains no cartilage, striped muscle, or other heterogeneous constituent. We may therefore exclude the very interesting type of mixed congenital tumours which has been worked out by Wilms, and is best known gynæcologically where it appears in the form of the "grape-like" sarcoma of the cervix met with in early life. Unlike the tumours of Recklinghausen, which develop actually out of Wolffian rests, these tumours are shown by Wilms to arise from cell groups which have become aberrant in a still earlier and more undifferentiated stage of embryonic life, and to have used the Wolffian body and duct as the vehicle whereby they were

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carried down into the situation where they subsequently became malignant.

Having now, so far as I am aware, excluded all other reasonable possibilities, I give my positive reasons for my diagnosis. We are dealing with an abdominal tumour presenting complex features, some of which resemble sarcoma, others carcinoma, others endothelioma. Suprarenal tissue at once suggests itself as being, from its normal characters, the most likely type of tissue found within the abdomen to give rise to a tumour presenting these complexities. The histological details confirm this suggestion. They present a complex of characteristics so typical as to render my diagnosis not merely tenable but necessary. The most important points are—(1) the well-defined capsule; (2) the distribution of fibrous tissue septa within the tumour and the relation of the parenchymatous cells to them, the tendency to form parallel columns, circular islands, and irregular polygonal groups; (3) the character of the cells, their granular and vacuolated protoplasm and nuclei, their arrangement in large groups with polygonal cell outline, lightly staining protoplasm, a large spherical centrally placed nucleus, with frequently a well-marked and deeply-staining nucleolus, and sometimes a clear spherical yellowish globule; (4) the intimate relation of the cells to the blood- and lymph-channels; (5) the hyaline deposits and the pigmented cells. Most of these are well recognised features of suprarenal tissue quite apart from malignant disease, and it is of interest to observe that the ready tendency of suprarenal cells to assume a large polyhedral form with clear protoplasm, and to develop giant-cells and cell fusions, is well marked in artificially transplanted suprarenal tissue. This is excellently illustrated by Poll in the account of his transplantation experiments. But perhaps the most striking feature of some of my sections is the strong resemblance they bear to the zona glomerulosa of the normal gland.

In view of the somewhat arbitrary means which are often put forward as proof of a suprarenal rest tumour, I should like to make it clear that my diagnosis rests on the above grounds.

A study of the literature of the subject corroborates my view. Some writers do, indeed, make much of the presence of glycogen, for which I was unable to test, and others lay stress on early

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fatty degenerations and pigment granules. But I do not find that any classical authority on the subject lays down any essential condition which my specimen fails to meet. Both in the main features and in less important though striking characters, such as tubular appearances, I find a close correspondence between numerous other well-established cases and mine. Grawitz, for instance, in his article on the occurrence of these growths as kidney tumours, speaks of the marvellous resemblance which some portions of such a specimen bore to the structure of an adenoma of the thyroid: "In parts it consists of glandular or gland-like formations; in parts connective tissue predominates; in other places small cysts are found; in still others, angiomatous portions with vessels in a high degree of amyloid degeneration." Marchand, describing a malignant growth of the right suprarenal in a girl of 20, lays stress upon the frequency of giant-cells and syncytia, the characteristic distribution of the fibrous tissue, creating in its finer ramifications an alveolar arrangement, the cell vacuolations, and cell inclusions. Chiari's tumour was completely encapsuled, hæmorrhagic, cystic, and largely necrotic. The cells were in many places large, epithelioid, with large nuclei, and often polygonal in outline. In numerous places were groups of cells enclosed in a meshwork of connective tissue, and placed concentrically around a free lumen, thus giving rise to a strikingly glandular appearance. However, I do not think it is necessary to dwell longer on the histological resemblances between my case and the numerous instances which have been placed on record.

I now pass on to further confirmatory evidence, which I have obtained for myself. Owing to the kindness of Dr. Andrewes, the curator of our museum, I have been allowed to examine several very interesting specimens of renal and suprarenal growths which have not yet been catalogued, and permitted to microscope them *ad libitum*. Two of them which I now describe, with the permission of Mr. Langton and Mr. Walsham, are of unmistakably suprarenal character.

Case 2.—Miss B. B—, aged 35. The patient was first seen by Mr. Langton on September 23rd, 1898. In August, 1895, she had consulted a London physician, who diagnosed a moveable kidney. For many months previous to seeing Mr. Langton she

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had noticed a lump in the left hypochondriac and lumbar regions, which latterly had increased somewhat rapidly in size. From time to time she had suffered attacks of pain, not excessively acute, in the left abdomen. Towards the end of August, 1898, however, she was seized with a severe attack of abdominal colic and sickness; hæmaturia from time to time, but not to any extent. Mr. Langton found an abdominal tumour "about the size of a cricket-ball but somewhat flatter, not tender, rather moveable in the lateral, but not in the vertical direction." Urine then normal; no microscopic evidence of blood; urates rather abundant; urea excreted about 270 grs. daily. He diagnosed a solid new growth of the kidney, and on October 1st, 1898, performed nephrectomy, finding the kidney moveable and deeply congested. The patient made a rapid recovery, returning home at the end of November. Mr. Langton's further account of the patient is as follows:—"I saw the patient again in August, 1899, with recurrence of a malignant growth, exquisitely tender, in the skin, of about the size of half a crown. The new growth was flat, and did not involve the deeper tissues to a great extent. I advised removal in order to afford the patient some ease, as any pressure from the dress gave her much pain. This was performed in September, 1899, and the parts brought together. This for the remainder of her life gave her complete ease, but she died in about ten months from dissemination. I did not see her again after the second operation."

The tumour, which was roughly kidney-shaped, measured 13 cm. vertically, 9½ cm. transversely, and 7 cm. in thickness. The convex surface is congested and somewhat nodular. On bisection the kidney is seen to be quite distinct from the new growth, to be separated from it by a capsule, and to rest upon its upper aspect. The lower end of the kidney is thinned out, and extends some distance downwards over the surface of the tumour. Microscopic sections taken parallel to the plane of bisection, and also from the convex aspect, confirm this relation, and show that renal tissue does not pass deeply into the tumour. The new growth is encapsuled; its cut surface is yellowish in colour, intersected by strands of fibrous tissue, and shows numerous patches and streaks of hæmorrhage, and also some necrotic softening.

Microscopic examination.—The tumour is largely necrotic,

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except at its periphery. In its typical parts it is composed of large cells, rich in protoplasm, which are divided by fibrous tissue strands, and by numerous blood-vessels and capillaries into groups and rows of varying size and shape, and are otherwise in immediate contact with one another. Their protoplasm is in the greater number of cells clear; their nuclei are rounded, centrally placed, and sometimes contain a lightly staining globule. Their general appearance is "epithelioid." The cells have a characteristic tendency to form a regular lining, which rests directly upon either side of the fibrous tissue ramifications, upon the vascular sheaths, and upon the outer aspect of the capillary endothelium. In these situations the cell outline is frequently columnar, the narrow base resting upon its fibrous or endothelial support, but the columnar changes into a flattened or polygonal outline in regions exhibiting more signs of compression. The more centrally placed cells of the larger groups between the supporting framework are usually of polygonal outline. The vessels are numerous, and show a marked tendency to hyaline and fibrous degeneration. Hæmorrhages are frequent, and there is also some homogeneous coagulated material, both intra- and extra-vascular. Fatty degeneration is localised and irregular. Renal tissue is only found near the capsule in those situations where the kidney is in apposition to the tumour. Here there is a good deal of connective tissue, and the growth is obviously not recent. Occasionally renal tubes and glomeruli may be found a short distance within the area of the tumour tissue, but are readily recognised as of a character alien to the latter.

Case 3.—George D—, aged 50, was admitted to St. Bartholomew's Hospital on January 23rd, 1899, under the care of Mr. Walsham. Five months previously he had noticed a swelling in the left side of his abdomen, which gradually grew bigger. He stated that he had not suffered any inconvenience from it, and gave no history of hæmaturia or any other trouble with his water at any time. Mr. Walsham examined the patient, and diagnosed a tumour of the left kidney. On February 7th he removed it, the operation being difficult owing to its size and adhesions, and the amount of hæmorrhage. All the hæmorrhage was stopped. The patient died on February 11th.

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Post-mortem.—No evidence of suppuration, peritonitis, or bleeding; intestines very distended; left suprarenal appeared normal; several enlarged lymphatic glands along course of left renal vessels; right suprarenal, kidney, and ureter, also bladder and urethra, all normal; liver normal. In the spleen was a spot which resembled a secondary growth. *Nil* abnormal in other viscera.

Macroscopically the tumour is so similar to that of Case 2 that it need not be specially described. The only difference is that it is somewhat larger, its dimensions being—vertically 18 cm., transversely 9 cm., thickness 10 cm.

The microscopic characters are also practically identical with those of Case 2. The renal tissue is very definitely marked off from the tumour; the cells of the latter are rather more compact, and arranged in somewhat larger groups than in the former case. There are fewer vascular channels filled with red corpuscles, and more dilated capillaries containing hyaline material. There are several patches of pigment, but I cannot say that it is anything more than altered and absorbed hæmoglobin.

Comparison of the Three Cases recorded.

Resemblances.—The essential characters of all three are the same, viz. the capsule, the distribution of fibrous tissue in relation to parenchymatous cells, the relation of the cells to the circulatory apparatus and the character of the cells, the coagulated exudation, and the typical character of the "epithelioid" cell.

Differences.—Whereas 2 and 3 are very similar, Case 1 appears more highly malignant than either of them. The cells are more varied in character, more granular, and more vacuolated; there are more striking cell-degenerations and cell-fusions and more giant-cells. There is a more general appearance of œdema, with more frequent dilated lymph and capillary spaces. The glandular appearances are very striking, and there is more hyaline degeneration.

Comments.—(1) It is interesting to note that although one would have thought, on histological grounds, that Case 1 had the least chance of cure, yet she is alive and apparently perfectly well twenty months after the operation, whereas 2 gave evidence

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of recurrence in ten months, and died about eleven months subsequently. Probably the site of the tumours had a good deal to do with it. Renal tumours appear to have readier access to the circulation and to disseminate more freely than those situated near the fundus uteri. It is noticeable that in Case 3, which was very much on a par with Case 2 at the time of the first operation on the latter, signs of dissemination were already present. (2) As regards comparative rates of growth, in no case have we a long history of a tumour, and it is very difficult to imagine what could have been the stimulating cause. In Case 1 we have a rather early menopause, and the growth appears to have started five or six years later, at a date when the commencement of the menopause would have been more usual. May it be suggested, in default of a better hypothesis, that, owing to the rather premature suppression of the nutritive and excretory functions to which menstruation is allied and subservient, local disturbances of nutrition arose in the vicinity of the suprarenal rest and stimulated it to malignant proliferation? In Cases 2 and 3 all that can be said in favour of a similar hypothesis of disturbed nutrition is that the kidneys are especially subject to such disturbances, towards which the accidents to which a moveable kidney is liable, in Case 2, and the age of the patient in Case 3, may possibly have been predisposing causes. (3) The more luxuriant type of growth of 1 may be due to the greater facility for unrestrained proliferation which is afforded to tumours arising from that situation. At the same time, though mechanical pressure and other physical causes may in a general way partly account for the differences between 1 and the other two cases, yet, taking Case 1 alone, we find that the differences in the morphology of the cells in various parts of it illustrate the fact, which is true of any complicated tumour in any situation, that such differences cannot be accounted for by variations in mechanical pressure alone. There must be other causes, local in action and chemical or chemico-physical in nature, which determine the varying shapes of cells and their protoplasmic and nuclear appearances. (4) The clinical symptoms of 1 are easily explained by its close connection with the uterus. The occurrence of hæmaturia in 2, and its other more acute symptoms as compared with 3, may be due to its more active connection with the vascular system, as

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evinced by the more abundant presence in the substance of the tumour of capillaries, arteries, and veins, all engorged with red blood-corpuscles.

I now proceed to consider what light my cases throw on questions of general interest.

I. Problems concerning the Normal Suprarenal.

(A) *Embryology.*—So many writers who have described suprarenal rest tumours have embodied in their account a summary of the various theories of suprarenal embryology, that I feel quite absolved from the necessity of compiling another. Agreeing with them all, that the embryology of the suprarenal is obscure, I confine myself to a few observations. As regards the relation of the suprarenal to the Wolffian body and duct, it is interesting to note that the latter appear on many occasions to have acted as vehicles for the conveyance of aberrant suprarenal tissue down into the pelvis. This is well illustrated by the site of suprarenal rests found in the broad ligament. Aichel has done useful work in cutting serial sections of a large number of broad ligaments in still-born females, and has shown the close connection of the suprarenal rests there found sometimes with the parovarium and sometimes with the paroöphoron. [I hasten to add that I do not in the least agree with the somewhat remarkable deductions he draws from these observations.] At the same time the fact that suprarenal rest tissue is so different from Wolffian rest tissue, and the fact that tumours derived from suprarenal rests are so different from tumours derived from Wolffian rests, point to the conclusion that the relation between the Wolffian body and duct and the suprarenal gland is an anatomical relationship of juxtaposition only, and not a causal relationship or a proof of common origin. It is, in fact, an illustration of the difficulty which seems to beset embryological work generally, that, owing to our limited histological means of cell differentiation, contiguity of cells is often the only indication available of a causal relationship, and is often illegitimately used as a proof of such. If, then, the exclusion of the Wolffian apparatus as the parent of the suprarenal gland suggests the origin of the latter from some tissue prior in order of differentiation, I confess I am not quite sure which of the

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many alternative theories to choose. Are we to say that the "epithelioid" character of suprarenal tumour-cells should incline us to prefer an epithelial rather than a connective-tissue origin, and suggest the somewhat vague "cœlomic epithelium"? Or are we to invoke to our aid that mammalian mystery, the pronephros? I do not know.

The only other embryological point I wish to mention is this: normal suprarenal rests often only exhibit one of the types of suprarenal tissue, sometimes the cortical, sometimes the medullary; suprarenal tumours frequently exhibit relationships characteristic of both types of tissue, although, as may be well seen in my first case, the tumour-cells present gradual stages of transition from the one type of arrangement to the other. These considerations seem to me to offer some slight support to the view of those embryologists who hold that cortex and medulla are of identical origin.

(B) *Internal secretion.*—The majority of authorities on suprarenal rest tumours call attention to the presence in parts of their specimens of an alveolar arrangement, together with tubular appearances, which, altogether, provides an interesting resemblance to a secretory gland. This feature is very well exhibited in my first case. Hence the question arises, Do suprarenal tumours throw any light on the supposed secretory functions of the normal suprarenal gland? I am aware that it is dangerous to argue from the abnormal to the normal. The evidence, such as it is, derived from observation of my own cases, is as follows:—Tubular appearances found in highly degenerate parts prove nothing. They are obviously to be explained by cell-fusions with the dropping out of the central part, cell-vacuolations, and the like. Nor, again, do the tube-like appearances found in the regions of dilated capillaries prove anything more than that the tumour-cells have a tendency to encircle the vascular and lymph-channels. The most interesting glandular appearances are those which occur where the nutrition is fairly good and where dilated capillaries do not dominate the scene; these parts are to be found sometimes peripherally, sometimes deeply situated, and then contained within one of the broader strands of fibrous tissue. The suggestion is, merely tentatively, of course, that whereas in the normal suprarenal the circulatory system is so elaborate and so perfect that there is free escape for the

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contents of every secretory cell directly into the proper circulatory channels, and therefore no necessity for an elaborately glandular arrangement; in a tumour, on the other hand, with its very imperfect organisation, the cells, still obedient to their secretory instinct, endeavour, on the analogy of other glands whose secretion is not utilised in the immediate vicinity of its production, to build up a more complicated glandular arrangement with a view to the collection of their secretion and the conveyance of it to places where it may find its proper exit. Two other points just worthy of mention are—(1) the very commonly occurring hyaline coagulated material in suprarenal tumours may represent an imperfectly elaborated form of suprarenal secretion; (2) extracts of suprarenal tumours have not been found to produce on animals the physiological effects of extracts of normal suprarenal medulla. This observation is in accordance with the usual clinical absence of toxic symptoms in suprarenal rest tumours.

(c) *Vascular relations.*—The intimate relation of the normal suprarenal to the vascular system is well illustrated by the close affinity of suprarenal tumour-cells for the circulatory channels; wherever they can they arrange themselves in a regular row around the vessels, and come in direct apposition to the endothelium of the capillaries. Bearing in mind the observation of Manasse, that even in the normal gland suprarenal cells may actually replace in part the endothelium of the capillaries and even project into the lumen, I have sought for corroboration of these phenomena in the cases I have described. I do, indeed, find tumour-cells directly bordering upon and actually growing into dilated capillaries, but as these parts are obviously degenerative, they cannot be adduced as evidence of a normal relationship.

(d) *Tubular appearances.*—Tubes are occasionally found in the normal human suprarenal, and are quite common in many other mammals, particularly the horse (Marchand). The very frequent appearance of tubes in suprarenal new growths indicates that when found in the non-proliferating organ they are not necessarily of extraneous origin.

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II. The Pathology of New Growths of the Suprarenal Type.

(A) The diagnosis of renal tumours thought to have originated from a suprarenal rest is facilitated by comparison with a suprarenal tumour which has originated in the true pelvis, and therefore far removed from any possible contamination with renal tissue. Hence we can definitely dismiss the view that renal tumours conforming to the type of Martha B— are after all only a peculiar form of renal carcinomata, and can further state with confidence that tubular appearances such as those of Martha B— do not prove a renal origin.

(B) The diagnosis of tumours of the suprarenal body is also facilitated. Just as suprarenal tissue may be included in the kidney, so renal tissue may be included in the mass of the suprarenal glands. Hence tubular appearances in certain malignant tumours of the suprarenal have been supposed by some to be due to contamination with renal tissue. But probably no one would care to hazard the suggestion that a bit of renal tissue is likely to be found in the pelvis enclosed within a suprarenal rest, and apart from the extreme remoteness of such a contingency, the obvious homogeneity of the "tubular" parts of Martha B— with the rest of the tumour is good evidence that similar appearances, when found in growths of the suprarenal body, are suprarenal and not renal in origin.

(C) *The question of renal endotheliomata and angiosarcomata.* —It has often been objected that many so-called suprarenal rest tumours of the kidney really are one or other of the former types; and so, undoubtedly, many of them are. After Grawitz, persons seemed to lose their heads over suprarenal rests, and attribute every and any sort of tumour found in the kidney to that origin—a method of procedure which no one more strongly condemned than Grawitz himself. Now, my three cases illustrate very well the similarity between certain parts of suprarenal tumours and angiosarcomata or endotheliomata. [I cannot here enter into the controversial difficulties raised over these two terms.] But my point is this: to diagnose a suprarenal tumour those features possessed also by many sarcomata and endotheliomata—vascularity, aggregation of cells around a meshwork of capillaries, close relation of cells to lymph spaces, rapid

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fatty degeneration, presence of glycogen, etc.—do not suffice. We must, in addition, be able to produce parts of the tumour which exhibit a definitely suprarenal structure. The kidney tumours which cannot satisfy this criterion, whatever else they may be, are not derived from suprarenal rests; those which can are.

(D) *Compensatory hypertrophy.*—It is sometimes alleged that the development of a suprarenal rest into a new growth is due to a defect in the proper activity of the suprarenal gland. The three cases I have examined do not support this view. In none of them was there any clinical evidence prior to operation, or any evidence in the course of the operation or *post mortem*, of suprarenal disease. Martha B—, twenty months after the removal of her tumour, is still alive and well, and therefore, presumably, her suprarenals are still performing their normal functions. Miss B. B— died of disseminated recurrence, and not of suprarenal disease. Both suprarenals of George D— were found *post mortem* to be normal.

Nor, again, do my cases lend any support to the view that, owing to the supposed close relationship between the functions of the suprarenal and certain of the regulative or nutritive functions of the sexual organs, deficiency of the latter may give rise to compensatory hypertrophy of the suprarenal gland or of a suprarenal rest. I allude to such cases as that of Marchand's of an adenoma of a suprarenal rest in the broad ligament, together with hyperplasia of the adrenals, in a pseudo-hermaphrodite aged 50. He thinks that these growths "can hardly have been merely accidentally concurrent with the rudimentary development of the ovaries and the co-existent pseudo-hermaphroditism." But we can hardly deduce a general rule from a body presenting so many extraordinary freaks of nature, and I think that Marchand cannot well object to my suggesting that there is not yet sufficient evidence available to prove that ovarian defect leads to hypertrophy of adrenal tissue.

III. General Problems of New Growths.

(A) *Distinction between carcinoma and sarcoma.*—Suprarenal tumours illustrate very well the extreme difficulty which arises every now and then in being able to distinguish, on histological

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grounds, between these two classes of growth. It is easy to pick out from one and the same suprarenal rest tumour sections which look definitely carcinomatous, others, again, which strongly suggest sarcoma, and finally others which show transitional stages between the two types. Similarly with tumours from other parts of the body, most pathologists occasionally meet with the same difficulty, and feel compelled to suspend their judgment until they can find good local evidence of the starting-point from which the tumour arose. I may mention as three instances of the kind which I recently observed—(1) a malignant thyroid growth where the difficulty was cleared up by ultimately finding a spot showing the transition from adenomatous to carcinomatous tissue; (2) a maxillary tumour which was very doubtful until a connection was found with the epithelium of the antrum; (3) a tumour near the vulva, which was equally obscure until a small focus of abnormal epithelium was discovered in the neighbourhood. In suprarenal tumours the difficulty is solved rather differently. The complexity of the tumour is explained by the high degree of differentiation of the tissue from which it originates. And this difference of explanation raises an interesting question of first principles. Why are tumours so complicated, so annoyingly different from the classical pictures in elementary text-books? Is it because our embryology is all wrong, and so, failing to understand the genesis of our epithelium and our connective tissue, we cannot recognise the appropriate degenerative capacities of each? Or is the complexity due to varying conditions in the foreign environment of the invading tumour-cells? Or, finally, have we in reality failed to grasp the complexity of the starting-point? A cell which forms the starting-point of a neoplasm has not only an embryonic ancestry, but also a long record of past innocence in adult life. Even when we are not, as we are in the case of suprarenal rests, dealing with the tissue of a definite organ, the relationships of the adult life-history of a group of cells are numerous and complex. Then may they not, by virtue of these past relationships, carry with them certain formative influences which partially determine the type of the resulting neoplasm?

(B) *Endotheliomata.*—There is a tendency, well marked in Ribbert, which appears to be on the increase, to set down as endotheliomata many tumours which more conservative patho-

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logists would classify under one or other of the subdivisions of carcinoma or sarcoma. I do not attempt to enter into a general discussion of this question, but merely point out the utility of well-authenticated suprarenal rest tumours as a standard for diagnostic purposes, in so far as the endotheliomatous characteristics they in parts exhibit are a proof that such characteristics do not necessarily arise from the proliferation of the endothelium or perithelium of the blood- or lymph-channels.

(c) *Embryonic theories.*—Partly because the cells of malignant growths possess some of the properties of embryonic tissue, the view has found favour that the starting-point of malignant disease is a group of cells which have retained in the adult body their embryonic properties, the reason alleged for such retention generally being that the cells in question have been cut off in developmental processes from their proper sphere, and so failed to participate in the progressive changes leading to the stability of adult tissue.

This view is generally supposed to be particularly well adapted for congenital tumours. On the contrary, it seems to me there is no class of growths better suited than adrenal rest tumours to illustrate its high degree of improbability. Let us take such a tumour and consider it in the light of this theory. We are to assume that the growth originated owing to a retention in the "rest" of embryonic characteristics. Now as to the nature of those characteristics, and the exact part they played in the development of the tumour, we may consider three possibilities: (1) the "rest" retained in adult life the microscopic characters of embryonic tissue; (2) or we may suppose that whilst not necessarily possessing in its pre-malignant life histological features microscopically distinguishable from those of adult tissue, the "rest" retained an inherent embryonic capacity for proliferation, comparable, *e. g.*, to the latent capacity of mammary tissue to develop at puberty or in pregnancy; (3) or, finally, the latent embryonic capacity for development may be no more than the main predisposing cause, whilst the actual stimulus to malignancy is some pathological influence which finds in this "rest" its seat of election, because retention of embryonic susceptibilities has enfeebled its resisting powers.

But, as regards (1), it is not the rule for embryonic features, recognisable under the microscope as such, to be retained in

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suprarenal rests. Numerous records of such rests found in post-embryonic life state that they present the appearance of adult suprarenal tissue. Now the frequency of these rests is enormous. We are told that by patient search (Schmorl) they can be found in 92 per cent. of all bodies. Other observers say that by cutting serial sections of the infantile broad ligament they can be found invariably. Obviously I do not pretend to vouch for the histological characters of all these, but I do maintain that so many have been found presenting the adult type of tissue as to quite invalidate the supposition that displacement of tissue in embryonic life leads to a retention in the tissue so displaced of *demonstrable* embryonic features. (2) Nor has the embryonic theorist any right to impose upon us the "dormant" embryonic capacities of these rests on the analogy of normal latent tissues which do not develop until puberty, for example; for whatever the exact conditions under which a rest arose, the number of them is so large, and their usual situations are so constant, that we have every reason to assume a uniformity in the sum of their determining conditions, and therefore of their inherited capacities. But since not more than one in many hundreds of thousands develops into a tumour, the explanation of such a development cannot be found in a common heritage of embryonic capacities. The quite exceptional result must be due to a quite exceptional cause; and since we have not the slightest grounds for saying that the embryonic antecedents of any particular rest were different from those of any other, we have absolutely no justification for saying that the growth of the tumour was the direct outcome of inherited embryonic capacities. (3) The rarity of these tumours is also a strong argument against an intrinsically greater susceptibility of embryonic tissue. Take any living being and suppose him subjected to that mysterious influence which is provocative of malignant disease. Upon what particular bit of tissue in the person's body is the malignant influence likely to fall? Consider the probabilities. The chances are very strongly in favour of that person's abdomen containing somewhere a suprarenal rest. But not one out of a thousand tumours actually does emanate from such a source. In instances innumerable the malignant influence must have passed over the embryonic rest and selected some spot where the persistence of displaced embryonic tissue

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is merely a conjecture formed to meet the exigencies of the theory.

Hence, I take it, suprarenal rest tumours provide a strong argument against the validity of the embryonic theory; and the peculiar value of them lies in the fact that the type of tissue from which they originate is so common as to give us ample material for investigation, and therefore provide a wider basis for sound deductions than isolated chance observations. We might, indeed, by a piece of good fortune, come across a bit of cartilage in the midst of bone, and might be able to say of it that it showed no resemblance to the embryonic type and no signs of degeneration into a tumour; or we might, again quite by accident, meet with a scrap of tissue somewhere which, though quite without evidence of malignancy, had, by some strange freak of fortune, retained its embryonic character. But such discoveries, though very interesting, are too scanty and too heterogeneous to form a basis for argument; whereas with suprarenal rests it is different. We can here fairly challenge the embryonic theorist to prove his case. Here we have displaced embryonic tissue in abundance, and tumours resulting therefrom are a rarity; unless his theory can explain this type of tumour, it is difficult to see what claims it has to explain any other.

(D) I now come to displacement and "tissue tension" theories of new growths, theories which allege that the reason why cells assume a malignant degeneration is that they have been dislocated from their normal surroundings, that there has been a disturbance of "tissue tension," a removal of the restraining influence which, in the normal economy of the organic whole, inhibits every cell from proliferating to excess and invading the territory of its neighbours. It is impossible here to deal with all the details of Ribbert's theory, which is the best exposition of this view; the amount of controversial literature which he and his opponents have contributed to the subject is too copious to be dealt with briefly. I confine myself to the question as to how far the fundamental principles of this type of theory conform to the recognised facts of suprarenal rest tumours.

The first point that naturally occurs to one is this: aberrant suprarenals are extremely common; we should therefore expect

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to find, if displacement of tissue alone is a cause of malignant disease, that their malignant degeneration gives rise to an enormous mortality in embryonic life and early infancy. This, however, is distinctly not the case. Secondly, the vast majority of suprarenal rests never undergo malignant degeneration. Thirdly, an initial displacement occurring in embryo can hardly be considered the efficient cause of malignant disease occurring in patients who are frequently fifty or more years old. Fourthly, the situation of those rests which actually do become malignant is often particularly inoffensive, *e. g.* in the capsule of the kidney or between the layers of the broad ligament; and they are further secluded by being encapsuled. Under such conditions their position can hardly be a disturbing factor in their relationship with adjacent structures. For these four reasons it is impossible to sufficiently explain the origin of these tumours by the abnormality in situation of the aberrant tissue in relation to the rest of the organism.

So far I have been assuming that the disturbance in tissue tension occurs as between the suprarenal rest and adjacent structures. The other alternative is that the disturbance occurs between the component parts of the suprarenal rest itself. I purposely emphasise what I think is an obvious fact, that this is the only alternative: the disturbance must practically be either between the aberrant tissue as a whole and other tissues, or between certain component parts of the aberrant tissue and certain others. My reason for emphasis is that this point, simple though it is, seems to have been ignored even by the most important upholders of this theory, with the result, I venture to think, of vitiating their argument. The fallacy is this: beginning with sarcoma, as the simplest type of malignant disease, here we have, according to the theory, a disturbance in tissue tension between connective-tissue cells and neighbouring tissues. Now, whether right or wrong, that is clear enough; it is a tension between a definite something and an equally definite something else. Applying a similar theory to epithelial cells, we have the explanation of the origin of carcinoma. Then, as an after reflection, it is observed that, as carcinoma is a more highly organised structure than sarcoma, we have in carcinoma a disturbance in tissue tension of a more complex type. Further, and by analogy, a new growth of aberrant suprarenal tissue is

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due to the disturbance in tissue tension of the still more complex constituents of that structure. But such a structure, by its very complexity, is nearer akin to an organic whole, and therefore only very slightly predisposed to that disturbance in tension which gives rise to a new growth. Hence, by a further generalisation, we get our theory that the more complex a bit of displaced tissue, the less liable is it to be the focus of a new growth, and, if it grow at all, the more likely is its complexity to keep its increase within adenomatous bounds. All this may, for the moment, seem plausible, but it ceases to do so as soon as we recollect that we have by this time drifted into a loose and wholly unjustifiable use of the term "tissue tension." As applied to sarcoma and carcinoma it implied a definite relationship between epithelial or connective-tissue cells on the one hand, and certain equally definite adjacent tissues on the other; but when we come to our suprarenal rest, or, speaking generally, to our group of highly organised cells, which for that reason seldom proliferates, and still less frequently becomes malignant, the balancing factors between which the disturbance of normal tension arises are no longer clearly defined. Is it a tension between our complex cell groups as a whole and external structures? If so, as I have already explained, the theory is quite inadequate to explain suprarenal rest tumours. Then is it an internal tension between certain component parts of the complex cell group and certain others? If so, in order to make the theory intelligible, these opposing factors must be defined. We must have it clearly understood that we have a definite element (*e. g.* parenchymatous cells) which, overcoming the restraint of its normal tension, is no longer kept in equilibrium by its proper antagonist (*e. g.* the stroma), and hence degenerates into a new growth. Now my point is that this demarcation between the opposite components of the tension is not, as a rule, made clear. On the contrary, "tissue tension" is used loosely as a vague entity, a general property endowing a complex group of cells with a common attribute. And it is upon this loose and therefore unscientific usage of the term that is based the theory that the predisposition to new growth and the degree of malignancy thereof varies inversely as the organic complexity of the original focus.

If my objection is sound, I shall naturally be asked how it is

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that extremely careful pathologists have not recognised the fallacy. My explanation is this: "tissue tension," used in this loose sense, is a chimæra; it is not always recognised as illusory because it is a term suggestive of physical science. Because physical and chemico-physical relationships are at the bottom of all vital processes, and because "tissue tension" suggests such relationships, the term is allowed to pass as a semblance of sober reality. Merely regarded as indicative that cell growth is conditioned, amongst other things, by the ultimate laws of physics, the term is equally harmless and unfruitful; the mischief comes in when it is taken as an explanation of facts, as a theory of new growths, and of the conditions under which they arise. It explains nothing. It throws no light whatever on the mystery of that disturbance in the economy of the tissues with which all theories of malignant disease are alike confronted.

And now for the displacement theory pure and simple as between the component parts of the suprarenal rest itself. Somewhere ensconced in the abdominal cavity of an adult we have a tiny portion of aberrant suprarenal gland. Suddenly that aberrant tissue develops into a neoplasm. Is this development due to a displacement in the immediate environment of certain cells of that tissue and their subsequent unrestrained proliferation? For two reasons, in addition to the above theoretical considerations, I do not think that this hypothesis is a plausible one. My first reason is a general one, which, in this paper, I can only mention without discussing. I believe that the general applicability of the displacement theory has been disproved by Hauser, who seems to have conclusively shown that, in intestinal carcinoma at all events, malignant degeneration frequently does begin without any displacement of cells. My second reason is based on the characters of the suprarenal rest tumours I have examined. It appears to me, as it has appeared to other observers who have worked at their cases, that the cases I now bring forward show definitely suprarenal characteristics. We find in one and the same tumour the typical arrangement of fibrous tissue, the typical arrangement of cells in groups and columns, and the typical disposition of cells around the capillaries and lymph spaces. Moreover we are dealing not with an adenoma, but with an unmistakably malignant growth. And it is the young and

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actively growing parts rather than the older and more degenerate which present more strikingly the complexity of suprarenal features. Hence it appears to me an arbitrary, improbable, and insufficient explanation to assume that particular isolated cells, impelled by their displacement to a limitless growth, can, by virtue of *an escape from* the restraining influences of their immediate environment, have evolved a tumour of the intricate complexity presented by this type. I am aware that here I am trenching upon the chaos of controversy which rages upon the terms metaplasia, anaplasia, and the like. I do not wish to plunge into the vortex of that discussion, and I venture to think that, quite apart from it, the objection I have put forward is plausible on grounds of ordinary common sense.

Before leaving this subject I should like to protest against the common objection of sceptical criticism, that discussions of new growth theories do not matter very much, that they lead to endless verbal controversy and no practical result. On the contrary, I think the endeavour to arrive at a right theory is of the highest practical importance, provided we aim not at a final pronouncement but at securing merely the best working hypothesis to guide us in experimental work. I do not think Ribbert's theory is a good guide. I incline rather to the more general view that the starting-point of a neoplasm is a localised alteration in nutrition, that whereas in carcinoma and sarcoma this initial alteration is generally confined to a small group of cells of a particular type, in the case of suprarenal rest tumours it affects the entire complexity—still often of only microscopic dimensions—which goes to make up an aberrant portion of a suprarenal gland.

(E) Very briefly I may mention the ordinary surgical theory of injury or chronic irritation as the starting-point of neoplasms. I think that most people will concede that a "rest" tucked away securely and inoffensively, *e. g.* in the broad ligament or the capsule of the kidney, is about the last bit of tissue in the body which would be likely to be exposed to a lesion of such a kind.

(F) This leads me to definitely infective or parasitic theories. Here, again, I think it will be recognised that we should have to postulate an extraordinary wilfulness, a wanton caprice, on the part of the infective organisms, which should lead them to

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travel harmlessly through the body and finally select so out-of-the-way a situation for their abiding place. The curious deposits, cell-degenerations, and cell-inclusions to be found in my sections, preserved and stained in the ordinary way, appear to me a strong indication that the very heterogeneous and elaborately prepared demonstrations of so-called parasites are the product of a misdirected zeal.

(g) Finally as to theories of diathesis or cachexia. It is noteworthy that suprarenal tissue, even in aberrant "rests," is intimately connected with the vascular system; and for that reason it might be suggested that some toxin in the general circulation might, finding here its *locus minoris resistentiæ*, be the occasioning cause of malignant proliferation. But, as against this view, clinical symptoms do not lend any particular support to the conclusion that the commencement of a new growth of suprarenal type is preceded by a condition of auto-intoxication. The future will tell us whether further applications of Ehrlich's work on the blood will throw any fresh light on this problem. In the meantime considerations of the evidence available seem to point rather to the hypothesis that, though neoplasms do originate from an alteration in nutritive conditions, that alteration not only acts locally but is brought about by local causes.

I wish to express my deep sense of obligation to Dr. Champneys, Mr. Langton, Mr. Walsham, and Dr. Andrewes for the valuable material with which they have provided me, and for the very friendly and helpful interest they have shown in my work, which was carried out in the laboratory of St. Bartholomew's Hospital.

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DESCRIPTION OF PLATE V,

Illustrating Dr. A. Eastwood's paper on "The Occurrence in the Pelvis of Malignant Tumours originating from Adrenal Remnants." (Page 153.)

FIG. 1.—From Case 1 (tumour expanding the layers of the broad ligament and resting upon the fundus uteri). To show the tendency in some of the recently growing parts to produce tubular appearances. × 200.

FIG. 2.—From the same tumour. There is a large amount of material resembling the colloid secretion of the thyroid to be found both within and external to the capillaries. Some of the cells contain clumps of brown pigment, often with a bright spot in the centre; others exhibit large and degenerate nuclei. × 200.

FIG. 3.—The left half of this figure is also from Case 1; the right half is from Case 3 (tumour of left kidney). The illustration is typical of the more compactly growing portions of both tumours. × 200.

FIG. 4 illustrates the mode in which the cells invest the blood-vessels and, in the less compactly growing portions of the tumour, assume a columnar form. The figure is taken from Case 2 (tumour of left kidney). × 200.

The method of staining is van Gieson's. The drawings have been made by M. H. Lapidge, with the aid of the camera lucida.

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Fig 1.

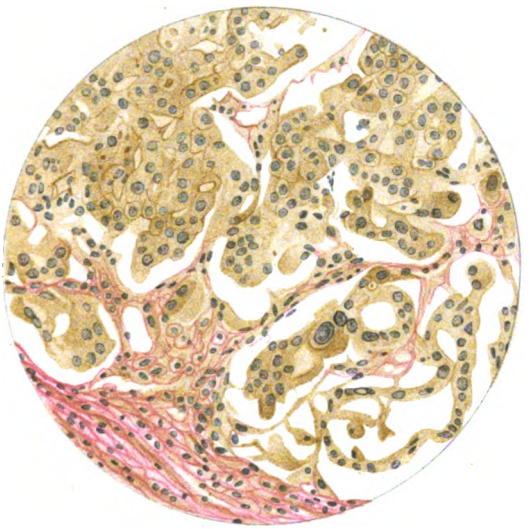


Fig.2.

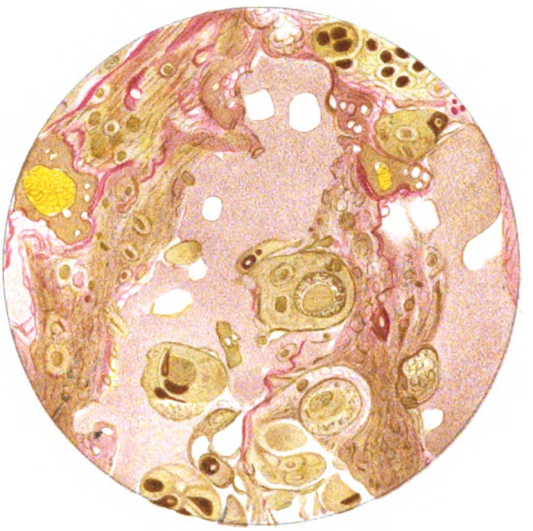


Fig.3.

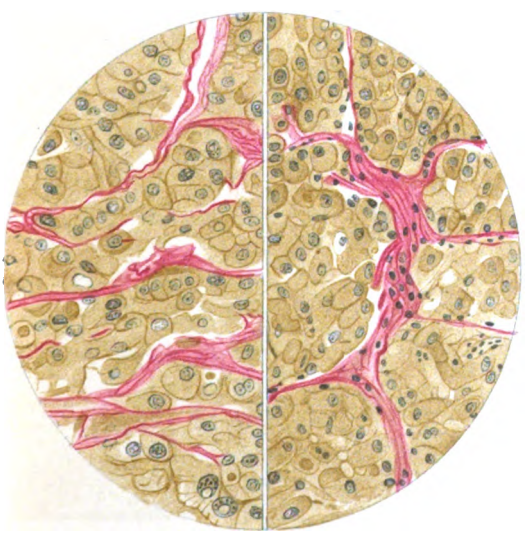
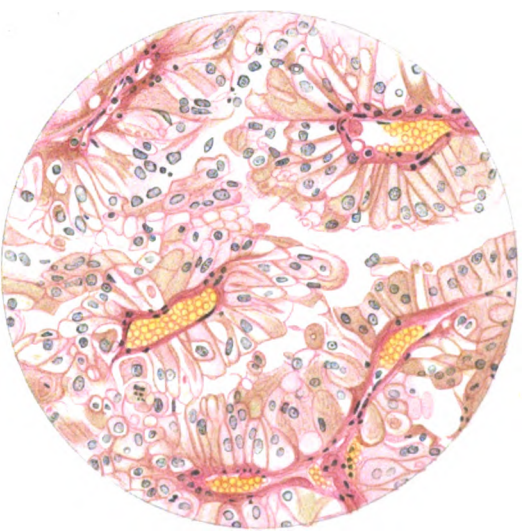


Fig.4.



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January 7th, 1902.

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14. *A renal tumour arising from adrenal remnants.*

By J. S. Fairbairn.

This specimen is put on record as an example of tumour formation in the hilum of the kidney, showing on microscopic examination a very close repetition of the structure of the zona fasciculata of the adrenal body.

The naked eye appearance of the specimen is briefly as follows:

It measures 4 by 4½ by 3½ inches, and consists of a rounded tumour contained within the renal capsule, and stretching the kidney over its outer surface. Except where the ureter and vessels, with the surrounding fat, form a slight break, the surface of the kidney is directly continuous with that of the tumour.

The growth is slightly nodular on its surface, showing small projecting bosses, with scar-like depressions between, most marked at the pole opposite the kidney.

On section (which was made after hardening in Kaiserling's solution) it is seen to be made up of yellowish-white masses, arranged roughly in convolutions round the periphery, and separated by strands of translucent connective tissue, which towards the central part forms a firm mass of almost cartilaginous hardness (the hardness probably the result of the preservative reagents). From this firm mass the strands run out to join the capsule, where the larger ones form the puckered depressions noted on the surface, while between them the proper tissue of the tumour forms the slightly projecting nodules.

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The growth is firm and homogeneous in the cortical part, and slightly softer and looser in texture in the deeper parts; here and there is some slight staining from effused blood.

The capsule is thin and fibrous, showing small vessels cut across in it; it is continuous with that over the kidney, and also passes inwards at the hilum, where it forms a well-defined band between the growth and the structures of the hilum, but becomes lost to the naked eye between the thinned-out portion of the kidney and growth. The kidney, except for its compression by the tumour, does not show any abnormal change. The renal structure is very sharply differentiated from the tumour structure, even where the kidney is so thinned out that there is little more than capsule left; the line of demarcation between the two tissues is fairly regular, but here and there may be noticed small processes of growth projecting into the kidney substance.

Microscopically the growth is found to be made up of epithelial cells, divided into rounded or polyhedral masses or into columns and narrow bundles by fine connective-tissue septa. The most frequent arrangement of these cell groups is that of long narrow columns, and is best seen in sections taken from the periphery of the growth, where they appear to run approximately at right angles to the surface. In some places these columns are made up of fine parallel bundles of only one layer of cells in thickness, and between each bundle a fine thread-like septum can be distinguished. Columns of cells of two or three layers of cells in thickness are, however, more frequent. In some parts of the sections there is a tendency for these bundles to become slightly separated from one another, leaving a space between, but this is probably an accident in the preparation. The rounded or polyhedral masses are well seen in those parts of the section, showing the edge of the growth where it adjoins the kidney; they contain more layers of cells than the columns, but are separated from one another by the same fine connective-tissue threads.

In more central parts this arrangement of cell groups is not so well seen; the cells are rather broken up irregularly into masses of varying sizes and shapes. The cells retain the same type in all parts of the growth where the original structure is preserved. They are for the most part cubical, sometimes poly-

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hedral, with a deeply stained rounded nucleus. The cell protoplasm is granular, stains lightly, and the cell outlines often indistinct. The rounded deeply stained nuclei are the most prominent feature in the tissue; they are very regular in shape, though they vary considerably in size, and show a well-marked intra-nuclear network.

In some places there is a considerable invasion of wandering cells.

The larger connective-tissue strands appear as hyaline bands, containing many vessels with well-marked muscular walls, and filled with blood-corpuscles. These larger bands show little sign of fibrillation, and contain but few cells—plain muscle and fibrous tissue cells, with here and there groups of included epithelial cells and leucocytes. The finer trabeculæ simply show long thin fibres with a few fibrous tissue cells, the finest strands apparently consisting merely of elongated cells with fine branching processes.

Where the growth abuts on the kidney there is a very sharp line of demarcation between the deeply stained kidney structure and the more lightly stained growth, and between them a fine band of fibrous tissue can be made out, though in some places this is so thin as not to be more than that separating the columns of cells in the growth itself. There is also a certain degree of small-celled infiltration. Where this fibrous tissue band is well marked it contains vessels of considerable size and isolated renal tubules, so that it appears to be formed partly at the expense of the kidney substance; it is also, however, joined by the fine strands between the cell columns.

There are several spaces with fibrous tissue walls filled with colloid or coagulated material; these, however, only occur in the portion of the growth immediately adjacent to the kidney, and may therefore be due to inclusion of renal structures, and not to any formation by the new growth.

No processes of cells can be seen pushing their way into the kidney, nor can any isolated masses of tumour-cells be recognised among the kidney structure.

The isolated renal tubules seen at the boundary of growth seem to be cut off by a new fibrous tissue formation occurring at this part.

The kidney shows only the changes due to compression; the

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tubules are flattened out and squeezed together, and the cortical layer is narrow and shows few glomeruli. There is no new formation of connective tissue, and the glomeruli show no fibroid change.

The kidney was removed by Mr. Bland-Sutton from a married woman of 42, who was admitted to the Chelsea Hospital for Women on account of an aching pain in the left side of six months' duration. A moveable "lump" in the left flank had been noticed for about five months.

The abdomen was opened in the middle line, and the right kidney found to be normal; the left was enlarged and cystic, and thought to be hydronephrotic. The abdominal wound was closed, and a lumbar incision made over the left kidney. A trocar was put into the tumour with the idea of emptying it, but nothing except blood escaped. On withdrawing the trocar there was quite a gush of blood, just as if a vein had been tapped. The kidney was then shelled out, its pedicle ligatured, and the whole mass removed.

The patient made a satisfactory recovery.

January 7th, 1902.

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15. *Congenital malformation of heart; diverticulum of right ventricle.*

By C. H. Fennell.

Eva M—, aged 8, was admitted to the Hospital for Sick Children on August 29th, 1901, complaining of cough and dyspnœa. On admission she was markedly cyanosed, and much clubbing of the fingers was noted. The area of deep cardiac dulness extended for a distance of three fingers' breadth on each side of the sternum; at the base of the latter an ill-defined systolic murmur was audible. Abundant bronchitic sounds were heard all over the left side of the chest, which was somewhat shrunken. The sputum contained tubercle bacilli. Signs of tubercular mischief developed in the right lung, and on

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September 26th the child died suddenly from an attack of profuse hæmoptysis.

The heart weighs 5 ounces. Its deviations from the normal type are for the most part those not infrequently met with, but the feature to which I would call attention is a diverticulum from the sinus of the right ventricle, about the size of a small walnut, and situate at the front of the right end of the margo acutus. The enclosed cavity is continuous in front and to the left with that of the ventricle, and is lined by columnæ carneæ. Its muscular wall is thicker than that of the sinus, and, as is seen on microscopical section, consists of practically normal cardiac muscle.

As regards other points of malformation, the septum ventriculorum is deficient, the large aorta arising from both ventricles. The sinus of the right ventricle is marked off from the conus by a definite narrowing, over which the endocardium is thickened. The pulmonary artery is small, and its valve bicuspidate. In thickness the left ventricle considerably exceeds the right. The foramen ovale is pervious but valvular; the ductus arteriosus barely allows passage to the finest bristle. The tricuspid valve shows thickening of its curtains. Over the diverticulum the pericardium is slightly thickened. The abnormal heart-dulness appeared to be due in part to the mesocardial position sometimes assumed by malformed hearts.

The valve of Thebesius takes the form of a thin hood-shaped process floating free in the auricle, and tethered to its original attachment by long slender filaments.

The fatal attack of hæmoptysis may be attributed to a ruptured aneurysm of the pulmonary artery, the size of a small hazel-nut, which was found in a vomica of the left lung.

I have been unable to find any account of a malformation similar to that of the right heart, in the Society's 'Transactions' or elsewhere. The congenital diverticula hitherto described have, so far as I can discover, been apical in position, recalling the bifid chelonian heart.

I am indebted to Dr. A. E. Garrod for his kindness in allowing me to show the specimen. *January 7th*, 1902.

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16. *The transmission of hæmolysins from ascendants to descendants.*

By William Bulloch.

Congenital immunity is a property which is transmitted from parents to offspring, and is, strictly speaking, hereditary.

A female who has *acquired* an immunity against an infection may also bear a child which proves to possess a certain degree of immunity. In man this has been observed in the case of variola (Lereboullet, Buchner) and vaccinia (Burkhardt, Chambrelent); in animals, after vaccination, against anthrax (Chauveau), symptomatic anthrax (Arloing, Cornevin, and Thomas), and other diseases.

Observations of this category are divisible into two groups, which differ fundamentally.

1. The mother acquires the immunity *during* the gestation.

2. The maternal immunisation took place at a period *anterior* to the conception.

If the mother is immunised during pregnancy the fœtus may also participate actively in the process, so that it is only for cases in the second group that an hereditary transmission of the immunity can be admitted. This transmission may be due, not to an heredity in the ontogenetic sense, but merely to a transference of the maternal antibodies through the placenta, and in this way the fœtus would become passively immunised.

Now, whatever theoretical and clinical evidence—and the latter is conflicting—has been advanced in support of the one or the other of these views, the transference of the problem by Ehrlich to the domain of experimental inquiry has marked a distinct advance.

As is well known, Ehrlich (1) in 1892 published his first communication on the transmission of the immunity from parents to offspring, basing his conclusions on immunisation experiments with ricin, abrin, robin, and the bacillus of *rouget des porcs*. This paper was followed in 1894 (2) by that on tetanus immunity.

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The main conclusions reached by Ehrlich were—

1. That an immune father does not beget immune offspring, *i. e.* the idioplasm of the sperma is not able to transmit the immunity.

2. That an immune mother bears immune young, but the immunity is not ovigenic, and is therefore not truly hereditary.

3. That the immunity of the descendant is derived from the placental passage of maternal antibodies, and the immunity is transient, lasting not longer than three months.

4. That the milk of the mother is the real agent which transfers the immunising substances to the body of the descendant.

5. That the immunity *increases* up to the time of weaning, and then rapidly diminishes and disappears.

These conclusions, so fundamentally opposed to current teaching, were confirmed in the main by Vaillard (3), who experimented with tetanus, anthrax, Vibrio Metchnikowi, and Vibrio choleræ. While admitting that tetanus-fast mice are able to confer immunity to normal mice through the milk, Vaillard found that in the case of guinea-pigs and rabbits no appreciable degree of immunity is conferred in this way, so that he was unable to admit the general applicability of Ehrlich's experiments on abrin and ricin. Vaillard also found that rabbits immunised against anthrax threw immune young, and as there are no definite antibodies in the sera of such animals, he regarded the immunity as a property transmitted to the phagocytes, whereby they were able to englobe and destroy the virus. In this he definitely asserts an inherited aptitude of the cells.

Tizzoni and Centanni (4), Gley and Charrin (5), have asserted this cellular immunity with greater precision, and have quoted experiments to show that an acquired immunity may be inherited from the male ascendant as well as the female. In Tizzoni's experiments rabbits were immunised with the *virus fixe* of rabies, and he stated that—

1. The male can propagate by the sperma the immunity towards rabies which he has acquired.

2. The male may propagate the immunity to descendants by different females.

3. The immunity of the descendant is less than that of the father.

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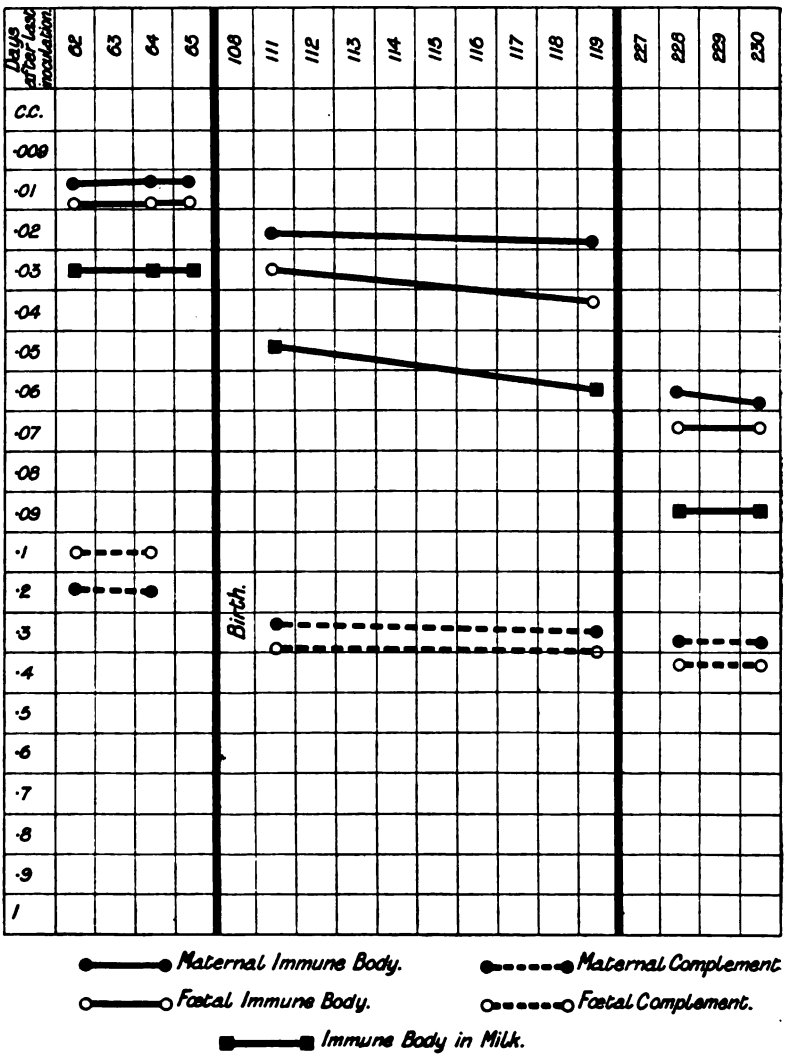
CHART.



The Chart shows the quantitative relation of the immune body and the complement in the maternal and fœtal serum, and in the maternal milk.

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4. The spermatogenic immunity is durable in contrast to the hæmatogenic or lactogenic, which is transient.

Similarly, Gley and Charrin, studying the immunity of rabbits towards Bacterium pyocyaneum, stated that the immunity was propagated from the male parent, although to a less extent than from the female.

Most recently, Dziergowsky (6) has tried to show that the antibodies and toxins do not pass the placental barrier, and that the fœtus acquires its immunity at a much earlier date from the liquor folliculi.

Ehrlich's results have been confirmed by Wernicke (7), and in part by Remlinger (8), who, however, like Vaillard, was unable to demonstrate the existence of antibodies in the blood of guinea-pigs or rabbits nourished on the milk of immunised females of the same species.

According to Metchnikoff the human species comes into the same category, and in them it is not possible to acquire immunity from the milk. A large number of experimenters have, however, demonstrated the existence of antibodies, mostly antitoxins, in the milk of actively immunised females.

Up to the present the only observations published on the transmission of hæmolysins have been those of Kraus (9). Hæmolysins are produced by the injection of the red blood-corpuscles of one animal into another animal of a different species. The serum of the latter acquires the property of dissolving *in vitro* the blood-corpuscles of the former, and, as is well known, this hæmolytic power is due to the combined action of two substances—the immune body which is created by the vaccinating substance, and the complement or alexine normally present in the serum.

Kraus immunised goats and rabbits with the blood-corpuscles of the dog or sheep, and on testing the milk found that it had no hæmolytic properties. Even when fresh complement in the form of normal serum was added, he failed to demonstrate in the milk the existence of immune body. He found, however, that the hæmagglutinins were excreted with the milk, although they did not pass to the fœtus through sucking. Kraus's experiments showed that the blood-serum of the young rabbits of immunised mothers is hæmolytic, and, as the hæmolysins did not pass out of the body in the milk, it is natural to suppose that

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they traversed the placenta, and in this way reached the fœtal body.

The experiments which I have made were in part communicated to the London Medical Research Club last spring, and, as the results differed very considerably from those of Kraus, I have repeated many of them with the following results. In all cases the hæmolysins were produced by injecting into rabbits the blood-corpuscles of the ox. In all cases the hæmolytic dose of the serum was determined on 2 c.c. of a 5 per cent. suspension of ox corpuscles in 85 per cent. saline solution, the time limit being one hour in the Ostwald water-bath at 37° C. and then eighteen hours in the ice safe.

The experiments were divided into four different groups:

1. The result of a union of a highly immunised male with a normal female.

2. The result of a union of a normal male with a female which was immunised subsequent to the conception.

3. The result of the union of a normal male with a female which was immunised prior to conception.

4. The result obtained by allowing normal young rabbits to suckle an immune mother.

GROUP 1.—However hæmolytic the blood of a male rabbit may be, the descendants show no such property if the mother was normal. This statement is based on the examination of the sera of the numerous progeny of eight immunised males.

GROUP 2.—Where the immunisation of the mother was begun after conception, it has not been possible to rear the stock on account of abortion. On examining the fœtus, however, the fluids were found to be highly hæmolytic, as one would naturally expect.

GROUP 3.—In the third group the mother was immunised before conception, and the determinations have been made in three such cases. In one of these exact figures were obtained in numerous descendants, the blood of the mother and the milk being likewise examined for complement and immune body respectively, and the degree of persistence of the hæmolysins, both in the mother and in the offspring, were determined. In one case the last injection of blood in the mother took place sixty-two days before the birth of the young, *i. e.* at least one month before conception occurred (gestation in the rabbit

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usually taking thirty days). Two days after birth the minimal hæmolytic dose of the native maternal serum for the standard quantity of ox blood was 0·2 c.c., the minimal hæmolytic dose of one of the litter of young being 0·1 c.c.; *i. e.* the native serum of the young may be more hæmolytic than that of the mother. This, however, was due merely to its containing a greater quantity of complement, for when the serum of both was inactivated at 55° C., and the amount of immune body alone determined by the addition of a standard quantity of normal guinea-pig's serum (0·2 c.c.), the minimal hæmolytic dose of both sera was found to be 0·01 c.c.

The milk in quantities of 1 c.c. produced no trace of hæmolysis. This, of course, did not preclude the presence of immune body. In fact, from the experiments of Ehrlich and others one would expect that the immune body would be excreted in the milk. On adding to the milk 0·2 c.c. of normal guinea-pig serum it was found to produce complete hæmolysis of the test dose of blood-corpuscles in the quantity of 0·03 of a c.c.,—that is, the milk contained one third of the quantity of immune body present in the blood. We thus see that the blood of the fœtus contained as much immune body as that of the mother. It contained more complement, this factor, of course, being independent of the mother; and third, although no complement passes out in the milk, the immune body does in considerable quantity—a fact which, as I have said, is denied by Kraus. As a result of interfering with this rabbit for bleeding and milking, she retaliated on the fourth day of the experiment by eating the whole of her young, eleven in number.

She was isolated and again covered, and brought forth another litter of ten thirty-seven days later, *i. e.* ninety-six days after her last inoculation of blood-corpuscles.

Seven days before birth the maternal serum was tested, and showed when fully complemented a minimal hæmolytic dose of 0·015 c.c. (instead of 0·01 c.c. in the first experiment). On the day of birth one of the young was found dead, and on testing its serum the hæmolytic dose was found to be 0·03, *i. e.* about half the maternal serum dose. The milk, again, was non-hæmolytic in its native state in quantities of 1·5 c.c., although when complemented with 0·2 c.c. guinea-pig's serum 0·055 c.c. lacked the standard quantity of blood.

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Since then the rabbit has had three litters, and in each case the milk has contained immune body, although in gradually diminishing quantities, as no immunising injection of blood has been practised upon her.

The passage of the immune body in the milk without a corresponding excretion of the complement raises an interesting point as to the relationship of the two in the maternal serum. As Ehrlich and Morgenroth have repeatedly emphasised, the avidity of the complementophilic group of the immune body is much less than that of the erythrophilic group. In such a case one may assume that the union of the immune body with the complement may be so slight that the two are dissociated; or it may be that the complement *in vivo* is chiefly intra-cellular, as has always been maintained by the French school, in which case it is easy to understand why the complement does not make its appearance in the milk.

Attempts have been made to settle the fourth point at issue, viz. whether normal young can acquire hæmolysins from suckling an immune hæmolytic mother. Up to the present I have not succeeded in accomplishing this experiment, as rabbits take very unkindly to the young of others. In regard to the question of the durability of the hæmolysins, the active immunisation is, as in the case of antitoxins, very persistent. After immunisation the minimal hæmolytic dose of a rabbit's serum when fully complemented was 0·0005 c.c. (for 2 c.c. of a 5 per cent. suspension of blood). Without any subsequent injections of blood the serum was still able to hæmolyse in a dose of 0·1 c.c. at the end of 387 days.

Where the young have been reared from an immune mother the hæmolysins have not been demonstrable in their sera after four months.

At no point, therefore, do these results differ from those obtained by Ehrlich on ricin and tetanus, and they have a certain amount of interest as showing that in a hæmolytic serum in which it is known there are two components, one of these which is essentially foreign to the organisms is excreted in the milk; whereas the other, the normal complement, is retained within the body of the mother.

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January 21st, 1902.

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17. *On the hæmolysin of* Bacillus megatherium.

By CHARLES TODD.

EHRLICH'S discovery that tetanus cultures contain not only a poison for the nervous system—the specific tetanising body (*tetanospasmin*)—but also a poison for the red blood-corpuscles (*tetanolysin*), which has the power of bringing about their hæmolysis *in vitro*, has been followed by the demonstration of similar hæmolysins in cultures of various other organisms, *e. g. B. pyocyaneus* (1), *Staphylococcus aureus* and *albus* (2), *B. diphtheriæ* (3), *Micrococcus tetragonus* (3), *Streptococcus pyogenes* (3, 4), *B. typhosus* (5), etc.

These hæmolysins seem peculiarly suited to the investigation of theoretical questions in connection with the composition and action of bacterial toxins and their antitoxins, as the tests can be carried out *in vitro* and yield definite colour reactions capable of very exact measurement; and this has been pointed out by

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Madsen (6), who, in his work on tetanolysin, showed the complete analogy of this body with the toxins of diphtheria and tetanus as determined by Ehrlich.

Tetanolysin, however, is not quite an ideal poison for such investigations on account of its great instability, which, according to Madsen (7), is such that the activity of a 4 per cent. solution kept at 20° C. had diminished in five hours to one half its former amount, and in twenty-four hours to one fifteenth.

It appears desirable, therefore, to employ a bacterial hæmolysin of more stable nature. This is met with in filtered cultures of *B. megatherium* (de Bary), which I have found to be powerfully hæmolytic for certain red blood-corpuscles, and, when kept at temperatures below 20° C., comparatively stable.

These cultures have the further advantage that they are not toxic for the ordinary laboratory animals, except in virtue of their hæmolytic power, so that the action of the lysin may also be studied *in vivo* (8).

The hæmolytic action of the bacillus was first observed in the course of some experiments with a sample of papain powder. It was found that the powder contained a strongly hæmolytic bacillus, which on isolation proved to be the *B. megatherium*.

A culture of the same bacillus was obtained from hay infusion, and the two races, together with one of *B. megatherium* (de Bary), obtained from Kral, of Prague, were used in the following experiments. These three, though showing slight cultural differences, appear to be all races of the same bacillus. Parallel experiments were made with the three bacilli, which were grown in alkaline broth in Erlenmeyer flasks at 37° C., and the hæmolytic power of the cultures was tested daily on a 5 per cent. suspension of guinea-pigs' washed corpuscles in 0·75 per cent. saline.

The following other members of the same group, all obtained from Kral, were grown in a similar manner and tested on guinea-pigs' corpuscles :—*B. subtilis* (Cohn), *B. mycoides* (Flügge), *B. butyricus* (Hüppe), *B. mesentericus vulgatus* (Flügge), *B. mesentericus fuscus* (Flügge), *B. gangrænæ pulpæ* (Arkövy). None of these gave any hæmolysis, which is interesting, as suggesting a simple method of differentiating *B. megatherium* from other members of this group.

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Formation of the lysin.—When the bacillus in grown in alkaline broth the formation of the lysin, which is in the main extra-bacillary, begins (as shown in Chart 1) between the second and third days, the amount rapidly rising to a maximum on the sixth or seventh day; after this it slowly decreases.

The temperature exercises an important action, and the best results have been obtained at from 35° C. to 37° C. Oxygen is essential, and though some growth takes place anaërobically, there is no formation of hæmolysin, hence a much stronger lysin was obtained by growing the bacillus in shallow layers of broth in Erlenmeyer flasks than in test tubes.

A somewhat high degree of alkalinity of the medium favours the production of the lysin, and the best results were obtained with ordinary peptone beef bouillon; this was made just alkaline to litmus, and then normal caustic soda added in the proportion of seven cubic centimètres per litre.

Parallel experiments were made by growing the same bacillus—

1. In six flasks of broth made just alkaline to litmus.

2. In six flasks of the same broth with the addition of seven cubic centimètres per litre of normal caustic soda.

After nine days in the incubator at 37° C. the cultures were filtered through a Pasteur-Chamberland filter and tested on a 5 per cent. suspension of guinea-pigs' corpuscles, with the result that the filtrate in the first case hæmolysed six times its volume, and in the second case forty times its volume of the suspension, showing that the formation of the lysin was approximately seven times as great in the more highly alkaline broth.

The composition of the peptone used appears to influence the resulting lysin to a remarkable extent. Witte's peptone was always employed, but different batches of this varied enormously in their suitability for the production of the lysin. On one occasion the lysin production of the three races of the bacillus became so small that I began to fear that it was losing the power of producing this substance. I tried passage of the bacillus on various media and employed many batches of broth to no purpose, but finally discovered that the trouble was due to the peptone, and on changing to another batch of the same peptone at once obtained an excellent lysin production.

Action of the lysin on the corpuscles of various animals.—The red blood-corpuscles of different species show a very great

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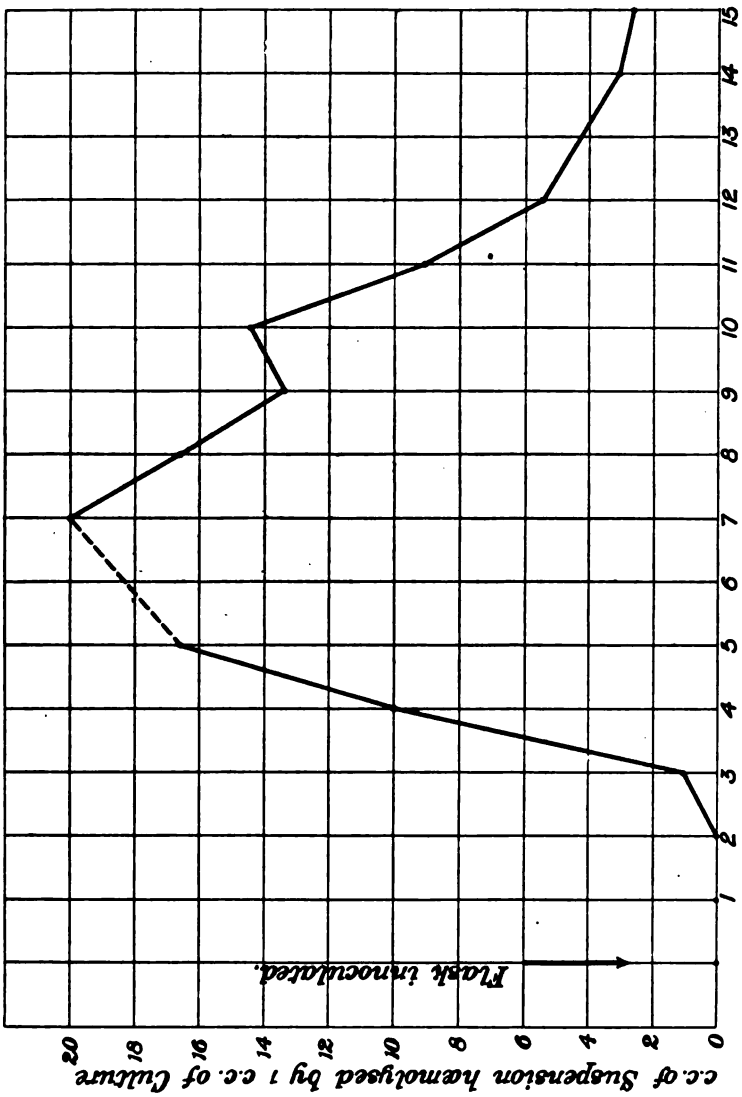
CHART I.



Showing the formation of hæmolysin in alkaline broth by *B. megatherium*.

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difference in the extent to which they are affected by the lysin, and those tried may be roughly grouped thus:

Guinea-pig Man Monkey	Highly sensitive.
Sheep Bullock Goat Pig	Moderately sensitive.
Dog Rat Rabbit Fowl Sparrow	Very slightly affected.
Donkey Horse	Practically unaffected.

In the case of the first group the following amounts of a particular lysin were required to produce complete hæmolysis of 2 c.c. of a 5 per cent. suspension of the washed corpuscles in 0·75 per cent. saline in one hour at 37° C.:

Guinea-pig . . .	0·08 c.c. lysin.
Man	0·30 c.c. „
Monkey . . .	0·50 c.c. „

Nature of the lysin.—Megatheriolysin resembles the toxins of diphtheria and tetanus in being mainly extra-bacillary, even young cultures filtered through a Pasteur-Chamberland filter being strongly hæmolytic. It is somewhat unstable at ordinary room temperature, but very much less so than tetanolysin. Thus in summer a filtered culture kept in the dark at room temperature for three weeks had gone down to one eighth of its original strength, while a culture kept in a cool room in winter, at temperatures varying from about 5° C. to 12° C., was found to have remained practically unchanged for ten weeks.

The hæmolytic power of the lysin appears to diminish somewhat rapidly shortly after filtration until it reaches a certain level, at which it remains more or less constant for a considerable time, thus resembling diphtheria toxin.

It is completely inactivated by heating at 56° C. for half an hour, and slightly lower temperatures markedly diminish its activity. In order to determine if this is true for corpuscles

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other than those of the guinea-pig, which were usually employed, samples of a particular lysin were heated for half an hour at 48°, 52°, and 56° respectively, and their action on the washed corpuscles of the guinea-pig, sheep, and bullock determined. These are shown in the following table, from which it will be seen that the lysin is inactivated for the corpuscles of these three animals at approximately the same temperature—56° C.:

Megatheriolysin (*P.* 4), *July* 13*th*, 1901.

Corpuscles.	Unheated.	48° ½ hour.	52° ½ hour.	56° ½ hour.
Guinea-pig .	50 vols.	33 vols.	2 vols.	0 vols.
Sheep . . .	11 „	8 „	4 „	0 „
Bullock . .	4 „	4 „	1 „	0 „

Numbers represent vols. of 5 per cent. suspension of r. b. c. s. hæmolysed by 1 vol. of toxin.

Corpuscles were washed once by decantation and suspended in 0·8 per cent. saline.

One hour limit at 36° C.

Neisser and Wechsberg showed that heating for twenty minutes at 56° inactivated staphylolysin, and Madsen, in the case of tetanolysin, found that twenty minutes at 50° C. brought about the same result. These two, therefore, with megatheriolysin, form a group of unstable hæmolysins easily inactivated by heat as opposed to the more resistent hæmolytic products of *B. pyocyaneus*, *B. typhosus*, and *S. pyogenes*.

I have failed to reactivate the inactivated megatheriolysin by sera, bacterial cultures, or any other method, and in this respect the lysin may be said to resemble eel-serum.

Experiments undertaken with a view to determining if the hæmolysis of the corpuscles of different animals is brought about by a common lysin, or if there is a specific body for the corpuscles of each race, have not as yet led to any definite conclusion, but there appears to be a balance of evidence in support of the view that the hæmolysis is not brought about by a common lysin.

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For instance, a certain quantity of the lysin was placed in contact with excess of washed guinea-pig's corpuscles and kept at 37° C. for three hours. The mixture was then centrifugalised and the supernatant clear but deeply hæmoglobin-stained fluid pipetted off. This was found to have almost completely lost its hæmolytic action on guinea-pig's corpuscles, but to be still active for sheep's corpuscles, though to a much less degree than before treatment.

In the converse experiment the lysin was exhausted for sheep's corpuscles and then found to be still active for guinea-pig's corpuscles.

Similar results were obtained in experiments with bullock's and sheep's corpuscles.

Again, if instead of using a suspension of one animal's corpuscles a mixture of equal parts of suspensions of the corpuscles of two different animals was employed, it was always found, in a large number of experiments, that less of the lysin was required to produce complete hæmolysis of the mixture than was necessary for the hæmolysis of the two separately.

For example, working with a particular lysin and suspension of very carefully washed corpuscles of the guinea-pig and sheep, it was found that—

1 c.c. suspension of guinea-pig's corpuscles required 0·40 c.c. lysin
1 c.c. „ „ sheep's „ „ 0·25 „ „

but the mixture required only 0·050 c.c. instead of 0·065 c.c., as would have been expected on the assumption of a common lysin.

The explanation of these results is by no means obvious, as the amount of the lysin necessary for the complete hæmolysis of mixtures is always less than should be necessary on the assumption of a common lysin, but greater than that required if we assume separate specific lysins. The supposition that the action of the lysin is brought about by a common "complement"-like body with specific "immune bodies" for the various corpuscles would explain the experimental results, and would be in accordance with what has been shown in the case of the hæmolytic sera, but the matter requires further investigation.

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Existence of an antibody in normal serum.—The antihæmolytic action of normal serum towards a bacterial hæmolysin was first pointed out by Ehrlich (9) for tetanolysin, and later by Kraus and Clairmont (10) and Neisser and Wechsberg (11) for other bacterial lysins. In the case of megatheriolysin various normal sera exercise a considerable antihæmolytic action, both towards the corresponding corpuscles and also towards those of other animals. Thus normal human serum protects human corpuscles against the lysin; the sera of the sheep and pig are strongly antihæmolytic towards their own corpuscles; donkey's serum has a marked action in protecting the corpuscles of the guinea-pig against the lysin, and this antihæmolytic power is increased by heating the serum for half an hour at from 63° to 65° C. No change takes place on heating for the same time at 60° C. Thus in one experiment it was found that a tube containing 2 c.c. of a 5 per cent. suspension of guinea-pig's corpuscles required 0·05 c.c. of the filtered culture for complete hæmolysis. If, however, 0·2 c.c. of normal ass's serum was added to the suspension 0·50 c.c. (*i. e.* ten times as much) of the filtered culture was necessary, and if the donkey's serum had been previously heated to 64° C. for half an hour 0·90 c.c. was required, so that the antihæmolytic action of the serum had been almost doubled by heating.

The serum of the guinea-pig is very slightly antihæmolytic towards its own corpuscles, but when heated for half an hour at 63° to 64° C. it becomes strongly so.

It is not easy to see any explanation of this increase in the antihæmolytic action of normal sera towards a bacterial lysin on heating, and it is possible that it is merely a physical effect depending on an alteration of the osmotic conditions, as the temperature of heating is so near the coagulation point that the sera are quite viscid.

In this connection it is interesting to note that Hédon (12), in his work on the hæmolytic glucosides, has noticed that there appears to be a slight increase in the antihæmolytic action of normal sera on heating to 60° to 64° C.

Immunisation of animals.—To determine if injections of the lysin give rise in the animal body to an antilysin a preliminary test was made with three guinea-pigs. These each received three injections, viz. 1 c.c., 2 c.c., 4 c.c., at intervals of about a

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week; the injections were followed by local necrosis in all the animals. Eleven days after the last injection the animals were bled, and their sera tested. In each case the presence of an antibody in the serum was easily demonstrated.

The following is the protocol of one of the tests:

Test of serum of immunised guinea-pig (June 16th, 1901).

0·2 c.c. Immune Serum (guinea-pig) + 2·0 c.c. 5 per cent. suspension guinea-pig corpuscles.		0·2 c.c. Normal Serum (guinea-pig) + 2·0 c.c. 5 per cent suspension guinea-pig corpuscles.	
+ 0·4 c.c. toxin	No hæmolysis.	+ 0·4 c.c. toxin	Complete hæmolysis (1 hour).
+ 0·6 „ „	Trace of hæmolysis.	+ 0·6 „ „	
+ 0·8 „ „	Very slight hæmolysis.	+ 0·8 „ „	
+ 1·0 „ „	Slight hæmolysis.	+ 1·0 „ „	
+ 1·5 „ „	Marked but incomplete hæmolysis (1 hour).	+ 1·5 „ „	
+ 2·0 „ „		+ 2·0 „ „	
+ 3·0 „ „		+ 3·0 „ „	

In both cases the serum and toxin were mixed and allowed to stand 1 hour in the incubator before the addition of the red blood-corpuscles.

The guinea-pig not being a convenient animal for the production of an antiserum, both on account of its small size and from the fact that in this animal filtered cultures give rise to severe local necroses, a goat was immunised with a filtered culture of the bacillus (obtained from hay) grown ten days in alkaline broth at 37° C.

The immunisation was carried out by subcutaneous injections, beginning with 0·5 c.c., and gradually increasing up to 200 c.c., the animal being bled on the tenth day after the last injection.

The injections gave rise to a local swelling, and there was usually a slight rise of temperature on the evening following.

The serum of this animal, after immunisation, was found to be very powerfully antihæmolytic, 1 c.c. of the serum completely neutralising 17 c.c. of a filtered culture, this amount of

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the particular culture being capable of hæmolysing 1700 c.c. of a 5 per cent. suspension of guinea-pig's corpuscles in three hours at 37° C.

In this case the cultures of bacillus obtained from hay infusion were used for the immunisation, but the serum was equally antihæmolytic, both towards cultures of this bacillus and also towards those of the two other races, thus confirming the view that these three bacilli, in spite of slight cultural differences, were all races of the *B. megatherium.*

Another goat was also immunised by Kral's *B. megatherium* with similar results. The injections, though they give rise to a large local swelling, with rise of temperature, do not cause any necroses in the goat.

Action of the filtered culture on animals.—In guinea-pigs, when given *subcutaneously,* even in doses as large as 20 c.c., the filtered cultures do not produce death, but give rise to a large swelling with subsequent necrosis. The substance giving rise to this necrosis is destroyed by heating at 60° C. for half an hour, but does not appear to be neutralised, at any rate completely, by the serum of immunised animals.

The action of filtered cultures, when given *intra-venously* in guinea-pigs, is seen from the appended table:

Table showing results of intra-venous injection of filtered cultures of the Bacillus megatherium *in guinea-pigs.*

No. of guinea-pig.	Dose of filtered culture injected intra-venously.	Symptoms.	Result.
1	1 c.c. + 9 c.c. saline	Five hours later, hæmoglobinuria. There were no red blood-corpuscles in the urine	Lived.
2	2 c.c. + 8 c.c. saline	Five hours later, hæmoglobinuria. There were no red blood-corpuscles in the urine	Lived.
3	5 c.c. + 5 c.c. saline	One and a half hours later, hæmoglobinuria. Crystals of hæmoglobin and a few blood-corpuscles were found	Lived.
4	8 c.c. + 2 c.c. saline.	Three hours later, hæmoglobinuria. Crystals of hæmoglobin and many blood-corpuscles were present	Lived.

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No. of guinea-pig.	Dose of filtered culture injected intra-venously.	Symptoms.	Result.
5	10 c.c.	Two hours later, hæmoglobinuria; there were no blood-corpuscles. Three and a half hours later, hæmoglobinuria; many blood-corpuscles were present	Died in 12 hours.
6	10 c.c.	Hæmoglobinuria, hæmaturia, and epistaxis	Died in 10 hours.
7	10 c.c. + 0·5 cc. antiserum	No symptoms	Lived.
8	10 c.c. + 5 c.c. antiserum[1]	No symptoms	Lived.

[1] In this case the antiserum was given subcutaneously, and 24 hours before the intra-venous injection of the filtered culture.

The animals used were all approximately 500 grammes in weight.

The results depend naturally upon the strength of the culture, which in this case was very weak—10 c.c. being necessary to produce death. With smaller doses—from 1 to 8 c.c.,—the animals survived. A few hours after the injection the urine passed was a dark reddish brown, often of the colour of stout, and gave the oxyhæmoglobin spectrum. If urine was passed shortly after the injection, most commonly no red blood-corpuscles were present, but these generally appeared later, and with large doses were found in the urine passed quite early.

Using a more powerful filtered culture, 0·5 c.c. intra-venously was sufficient to cause severe hæmoglobinuria, with death in twenty-seven hours.

When mixed with a small amount of the antiserum, intra-venous injections, even of large quantities of the lysin, produce no hæmoglobinuria, and if the animals receive a subcutaneous injection of the antiserum the day before the intra-venous injection of the lysin, no hæmoglobinuria results, showing that the hæmolysis is brought about by a specific lysin and not by a simple chemical or physical action. In this connection it is interesting to note that in the rabbit—the corpuscles of which are only very slightly affected by the lysin *in vitro*—large

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intra-venous injections of the lysin produce no hæmoglobinuria.

Investigation of the lysin by Ehrlich's method.—For this purpose a modification of the method employed by Madsen was used. 1 c.c. of the lysin was placed in each of a series of small test tubes of 10 mm. diameter, and graduated quantities of antitoxin added to these. The contents of each of the tubes were made up to the same volume (2 c.c.) with 0·75 per cent. saline, and the tubes shaken to ensure thorough mixture, and placed in the incubator for half an hour. At the end of this time 2 c.c. of a 5 per cent. suspension of washed guinea-pig's corpuscles in 0·75 per cent. saline was added, and the tubes put back into the incubator and kept at 37° C. for three hours. They were then centrifugalised and the amount of hæmolysis determined by comparison with a standard tint scale, made by placing graduated measured amounts of the same suspension in similar tubes, making up to 4 c.c. with distilled water, and leaving these in the incubator for three hours.

This method is capable of yielding very uniform results if certain precautions are used.

The differences of tint are much more easily appreciated over a certain part of the tint scale (representing the hæmolysis of from about 5 per cent. to 25 per cent. of the above suspension), and it was always arranged that the hæmolysis to be observed should fall within these limits by using, if necessary, instead of 1 c.c. of the toxin, 1 c.c. of a dilution of the toxin to $\frac{1}{5}$, $\frac{1}{10}$, $\frac{1}{15}$, etc., as required, and the same dilution of the antitoxin, and multiplying the results accordingly.

The suspension of corpuscles employed was made by suspending a known volume of freshly defibrinated guinea-pig's blood in a large volume of 0·75 per cent. saline. The mixture was allowed to stand twenty-four hours in the ice-safe, the supernatant clear saline poured off, and fresh saline added so as to make the strength of the final suspension correspond to 5 c.c. of the defibrinated blood to 100 c.c. of the suspension.

As the sensibility of the corpuscles, however, varies considerably, both in different animals and also with keeping, etc., the testing of a lysin was, when possible, always completed on the same day, using the same suspension throughout. To ensure complete interaction between the lysin and antilysin, the tubes

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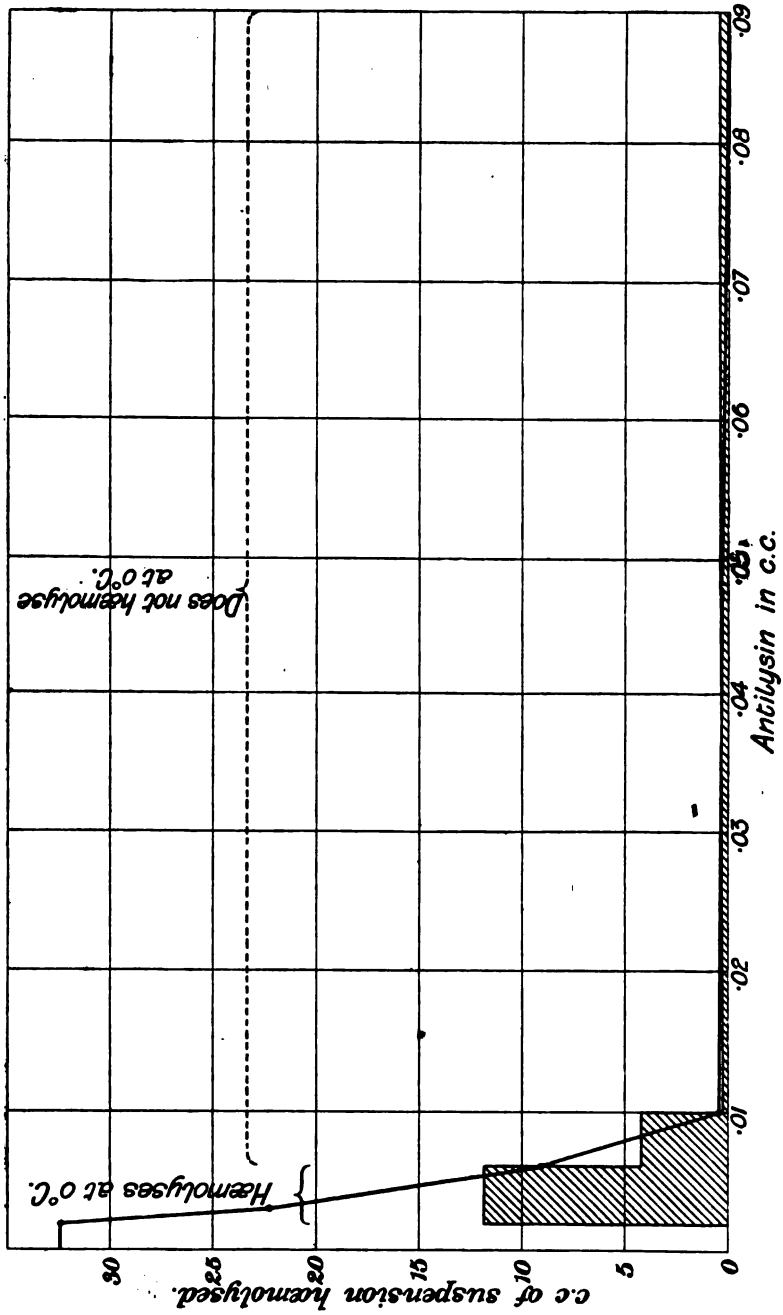
CHART II.



Filtered culture of *B. megatherium* (K.5) tested three days after filtration.

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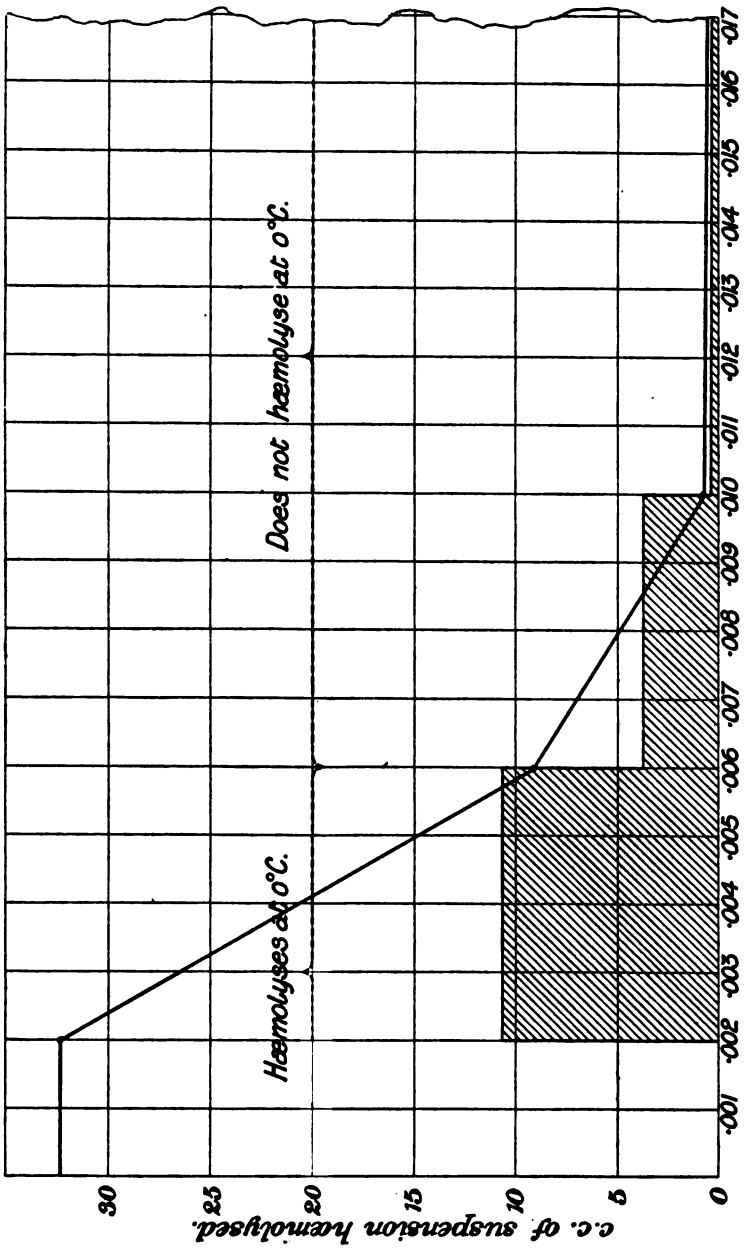
CHART III.



Filtered culture of *B. megatherium* (K. 5) tested three days after filtration.

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were at first left for an hour at 37° C. before adding the suspension, but this was found to be unnecessarily long, as the neutralisation takes place much more quickly in the case of megatheriolysin than found by Madsen for tetanolysin, and half an hour is ample.

With each test controls of toxin only were submitted to the same dilutions and kept for the same time in the incubator, but without appreciable loss of hæmolytic power.

Tests were made in this manner of several filtered cultures of each of the three races of the bacillus, and gave similar results.

The following table gives the figures obtained from the testing of a culture of *B. megatherium* (Kral) grown ten days in alkaline broth at 37° C., filtered through a Pasteur-Chamberland filter and tested three days after filtration :

Lysin K. 5. (*three days after filtration*), *January 23rd*, 1902.

2 c.c. suspension require 0·06 c.c. lysin for complete hæmolysis. Serum of Goat 2 used as antiserum.

+ 0	serum	hæmolyses	32	c.c.	suspension.
+ 0·0002	„	„	32	„	„
+ 0·0004	„	„	32	„	„
+ 0·0006	„	„	32	„	„
+ 0·0008	„	„	32	„	„
+ 0·001	„	„	32	„	„
+ 0·002	„	„	32	„	„
+ 0·003	„	„	22	„	„
+ 0·004	„	„	(22)	„	„
+ 0·006	„	„	9	„	„
+ 0·01	„	„	0·6	„	„
+ 0·04	„	„	0·4	„	„
+ 0·07	„	„	0·2	„	„
+ 0·08	„	„	trace		
+ 0·09	„	„	none		
+ 0·10	„	„	none		

These results are shown graphically in Chart 2, and on a larger scale in Chart 3.

In these charts the amount of hæmolysis effected by a c.c. of the lysin when partially neutralised by varying amounts

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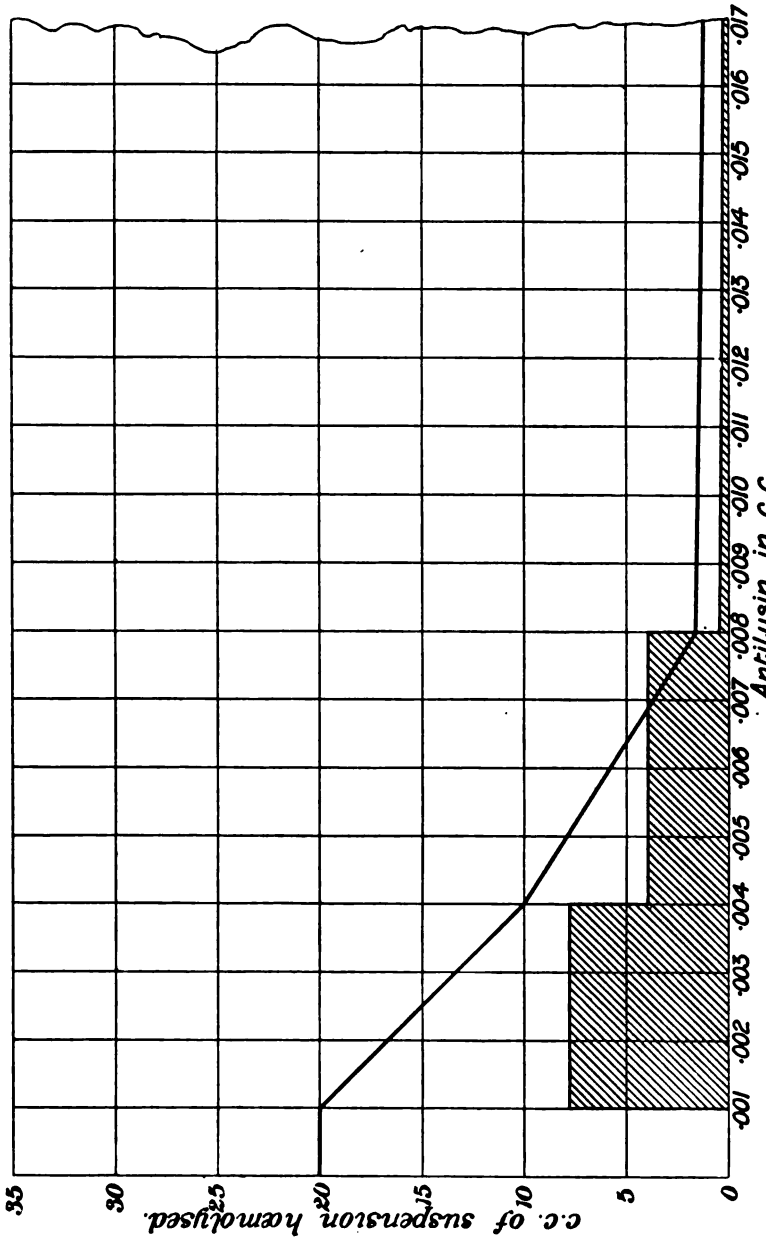
CHART IV.



Filtered culture of *B. megatherium* (K. 4) tested sixty-four days after filtration.

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of the antiserum is shown by the abscissæ of the simple curve, while the shaded portions represent by their area the distribution of the active body in the "spectrum" after Ehrlich's method.

Taking Charts 2 and 3 it will be seen that the addition of the antiserum at first (up to 0·002 c.c.) produces no diminution in the hæmolytic power, showing that the *prototoxin* (to use Ehrlich's terms) has been converted into *prototoxoid*, which, though it has no hæmolytic action, is still capable of neutralising antitoxin.

On the further addition of serum (from 0·002 to 0·006 c.c.) neutralisation takes place at a uniform rate, this region corresponding to the *deuterotoxin;* and on further addition (from 0·006 to 0·010 c.c.) neutralisation again takes place uniformly but more slowly, this corresponding to the *tritotoxin*. From this point on neutralisation takes place exceedingly slowly, and 0·08 c.c. has to be added before complete neutrality is obtained; this last region may, perhaps, be compared with Ehrlich's *toxone* region.

Chart 4 shows the same phenomena in another culture which was tested sixty-four days after filtration; in this the *deuterotoxin* has diminished in amount, owing to conversion into *deuterotoxoid*.

On comparing the spectra of megatheriolysin with those obtained by Madsen from tetanolysin two striking differences are observed, viz.:

1. In the case of megatheriolysin the *prototoxin* is so unstable that it is usually not met with in filtered cultures, having been entirely converted into toxoid.

2. The small fraction of the length of the "spectrum" occupied by the more active toxins in the case of megatheriolysin as compared with tetanolysin and diphtheria toxin.

Another interesting point in the study of the various components of the lysin is their action on the red blood-corpuscles at low temperatures (about 0° C.) In the following test 1 c.c. of the filtered culture was mixed with varying quantities of the antiserum; these were all made up to the same volume with saline, in small test tubes, and kept for an hour at 37° C. They were then cooled to 0° C., and equal quantities of cooled suspension of red blood-corpuscles added. After twenty-four hours at 0° C. the condition of the tubes was examined with the following result

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Hæmolysis at 0° *C.* (*K.* 5.)

Filtered culture, serum.		Result in 24 hours.
1·0 c.c.	0 c.c.	Very marked hæmolysis.
1·0 „	0·001 „	
1·0 „	0·002 „	
1·0 „	0·003 „	
1·0 „	0·004 „	
1·0 „	0·006 „	Slight but definite hæmolysis.
1·0 „	0·008 „	No trace of hæmolysis.
1·0 „	0·010 „	
1·0 „	0·02 „	
1·0 „	0·04 „	
1·0 „	0·06 „	
1·0 „	0·08 „	

Thus showing that while the *deuterotoxin* is capable of hæmolysing at 0° C. the *tritotoxin* and less active portions of the spectrum are not. This entirely coincides with Madsen's results for tetanolysin.

Conclusions.

1. In cultures of *B. megatherium* there occurs a specific lysin which has the power of hæmolysing *in vitro* the corpuscles of certain animals, notably those of the guinea-pig, man, and the monkey.

2. In the case of the guinea-pig, when given intra-venously, the lysin is capable of producing hæmolysis *in vivo*, causing severe hæmoglobinuria and death.

3. The lysin is somewhat unstable, and is entirely deprived of its hæmolytic action by heating at 56° C. for half an hour.

4. The formation of the lysin takes place best in somewhat strongly alkaline broth in the presence of oxygen at 37° C.

5. Many normal sera exercise an antihæmolytic action towards the lysin, and this action is markedly increased by heating to 63° C. for half an hour.

6. Subcutaneous injections of the lysin in animals give rise to a powerful antihæmolysin.

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7. By means of Ehrlich's method of partial neutralisation the lysin can be shown to yield a characteristic spectrum, analogous to those of tetanolysin and diphtheria toxin.

8. By this means the lysin may be divided into four parts :

(*a*) *Prototoxin :* Exceedingly unstable and usually found only as toxoid, even immediately after filtration.

(*b*) *Deuterotoxin :* Which is responsible for about three fourths of the hæmolytic action of the lysin and capable of acting at 0° C.

(*c*) *Tritotoxin :* Responsible for about a quarter of the hæmolytic action, and incapable of hæmolysing at 0° C.

(*d*) *A fourth body* having very slight hæmolytic powers and resembling, in its distribution in the spectrum, the *toxone* of diphtheria poison.

(This body is also incapable of hæmolysing at low temperatures.)

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November 5th, 1901.

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18. *The bacteriology of a case of rapidly-spreading gangrene without emphysema.*

By Harold R. D. Spitta.

So much has been written of late, and such a large amount of attention has been paid to the existence of anaërobic organisms associated with the various forms of gangrene, that to-night I venture to bring before you a few bacteriological notes on an interesting case of rapidly-spreading gangrene without emphysema which occurred in St. George's Hospital in September last.

The patient, a man aged 26, and a lift fitter by occupation, was admitted under Mr. Turner's care into the Oxford Ward on September 3rd, 1901, suffering, as the result of a lift accident, from a severe lacerated and contused wound of his left hand, involving a fracture of his four outer metacarpal bones and the lower third of his radius. The muscles, vessels, and nerves were extensively torn, and the whole wound much contaminated with dirt, though apart from this its aspect presented nothing unusual. The tissues being thoroughly cleansed, the proximal ends of the metacarpal were removed, and when the tendons had been united as far as possible, the ordinary surgical dressings were applied. His temperature, normal on admission, now rapidly began to rise, and twenty-four hours later indicated slightly over 102° F.; his pulse also registered 112, and on inspection of the parts it was evident that gangrene was fast setting in. There was practically no emphysema, and the tissues in the neighbourhood exhibited no obvious crackling or crepitation, though they were reddened, infiltrated, and slightly œdematous. One large bleb or bulla containing a small amount of serum was noticed on the spreading gangrenous edge, but nothing further of importance was observed. Pus was very scanty, and a small pellet only at this stage was sent over to the bacteriological laboratory for examination, which was at once taken in hand. Aërobic agar and broth tubes and a couple of anaërobic glucose-formate-agar and broth cultures were made, and, employing the modified Buchner's method with alkaline pyrogallate and a vacuum induced by a high-pressure

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water pump, were incubated at the body heat. Fresh and stained covers from the pus were then examined; these showed the presence in an apparently pure state of an organism about the thickness of the anthrax bacillus possessing rather square ends, non-motile and non-spore bearing, occurring singly, in pairs, rarely in chains, staining well with the ordinary aniline dyes, though not very satisfactorily by the method of Gram, and which was not acid- or alcohol-fast. Early the next morning—some eighteen hours after their inoculation—the aërobic and anaërobic cultures were examined. Though the former were sterile, those grown anërobically showed marked evidence of life. The evolution of gas in the deep stab glucose-formate tube was so excessive as to completely remove the plug, whilst the formate broth culture also showed an abundant growth with the formation of a thick, ropy precipitate or deposit. Both in fresh and stained preparations the two tubes contained an identical micro-organism, but at the time—chiefly for convenience—the organism from the broth culture only was employed. From this tube, then, aërobic glucose-agar and broth tubes, and a duplicate series of anaërobic cultures in milk, serum, glucose-formate-agar and bouillon, potato, gelatine, sugar-free agar and broth were made, one set being incubated at the room and the others at the body temperature. I also inoculated a 300 grammes guinea-pig with half, and a 320 grammes guinea-pig with 2 c.c. of the broth culture, both being into the peritoneal cavity. The same evening a series of cultures were also made to make quite certain that the same organism was present in both the original agar and bouillon tubes, but the consideration of these may be dismissed with the remark that, to the best of my ability, they were both microscopically and culturally identical.

Sixteen hours after inoculation the 2 c.c. guinea-pig died, and its fellow injected with a quarter of this amount seemed also to be ill and languid. The *post-mortem* on the 2 c.c. animal was made about an hour after its death. The notes made at the time are the following:—"Animal smells a little foul, abdomen is very much distended, and a large rent some four to five inches long, unconnected with the seat of inoculation, is present. The skin is infiltrated, œdematous, and rotten, though not emphysematous, and the fur comes off very easily.

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"*Subcutaneous fluid.*—This is in excess of normal; tissues are reddened, soft, and flabby. Isolated a thick, square-ended, non-motile bacillus about the size of the anthrax organism, which stains well with the ordinary aniline dyes, but with the method of Gram decolourises into granules rather easily. Made cultures in glucose-broth and glucose-agar, and cultivated aërobically and anaërobically at 37° C.

"*Peritoneal fluid.*—Abundant. There are signs of a recent peritonitis, and many yellowish flakes of fibrinous material are present. The peritoneum contains a fair amount of gas, which has a slightly fœtid odour. The intestines are dark in colour and distended. An organism, identical both in its staining and microscopical appearances to that described in the subcutaneous fluid, was found, and similar aërobic and anaërobic cultures were made.

"*Pleural fluid.*—Slightly in excess of normal. No other abnormalities found. The same microbe—though only in small numbers—was also seen in this fluid, and similar aërobic and anaërobic cultures were made and incubated at 37° C.

"*Heart blood.*—This was withdrawn from the left ventricle with a sterile pipette. An organism, apparently identical with the foregoing, was again found, and similar glucose-agar and broth cultures, incubated at the body temperature, were made under both aërobic and anaërobic conditions.

"*Spleen.*—This organ, though perhaps a trifle dark in colour, was not enlarged or otherwise abnormal, but it is to be regretted that owing to an oversight it was examined no further.

"All the other organs seemed healthy."

As an autopsy of this nature always necessitates the employment of so many cultures, it will not be necessary to discuss them individually, save briefly to remark that one species of organism only was isolated from all the secretions of the guinea-pig, and that its chief characteristics may be summed up in the following few words:—present, a rod-shaped, rather square-ended bacillus, non-motile and non-spore bearing, a true anaërobic gas-producing organism, which stained with all the ordinary aniline dyes, but indifferently when the method of Gram was employed; and further, when subsequently recultivated anaërobically outside the tissues at both the room and body temperatures, was identical, culturally and microscopically, with the original organism grown from the pus.

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Having demonstrated the pathogenicity of this anaërobic bacillus to guinea-pigs, attempts were now made not only to identify it, but also to ascertain its behaviour in atmospheres of HCO_2 and N, to test its fermentative properties on the various sugars and carbohydrates, and to investigate several points of morphological interest; but unfortunately the death of the organism, which occurred somewhat unexpectedly, cut short the desired series of experiments.

As far as could be ascertained, its optimum temperature was 37° C., but growth also took place at the room heat, though always very slowly. In *agar containing 1 per cent. glucose and ½ per cent. formate of soda* growth was always very rapid, and gas evolution abundant, though on this—as on other media—the organism died out very quickly, usually in a few days. In *glucose-formate broth* the bacillus always grew well, especially in the hot incubator. The medium in twenty-four hours was rendered densely turbid, and a thick ropy precipitate or deposit always formed. Gas production was also present, and a Durham's tube demonstrated this very efficiently. Ordinary *sugar-free broth and agar*, both at the room and body temperatures, also seemed to be suitable media, and gas in small quantities was always produced. On slope tubes the colonies were discrete, small, and circular, about 0·5 mm. in diameter, of a dirty grey colour, and the cultures seemed to have a slightly putrescent odour. In *milk* a growth could never be obtained, either at 21° C. or at 37° C., though several series of tubes were inoculated and reinoculated. On *potato* in the hot incubator the organism grew fairly well, forming an invisible film-like growth. *Solidified serum* at 37° C. seemed an especially good medium, the organism growing in the form of small, discrete, greyish colonies, about 1 mm. in diameter, but never producing any liquefaction. On all media the bacillus seemed to have a very short life, and the many unsuccessful attempts at preserving its vitality are much to be regretted.

Cases of spreading gangrene associated with marked emphysema are not uncommon, and in a recent paper Drs. Corner and Singer have briefly dealt with the subject. These observers conclude that Welch's *B. aërogenes capsulatus* and Fraenkel's identical *B. emphysematosus* are the organisms most commonly associated with the condition. But the present case does not

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quite correspond, either clinically or bacteriologically, with those described as due to a genuine infection with Welch's organism, the marked absence of emphysema being hardly in accordance with typical cases. In some respects, however, Welch's bacillus and the organism I was able to isolate resemble one another, but in the literature it is so very difficult to obtain definite statements as to the exact morphology of the *aërogenes* bacillus. For instance, Drs. Corner and Singer, in their recent paper, quote Welch in his Shattuck Lecture, where he says that *B. aërogenes capsulatus* may or may not liquefy gelatine, that it may or may not form spores, may or may not be capsulated, and so forth, none of which statements are reassuring. Then, again, with regard to the method of Gram, as applied to his bacillus, Welch states that on some occasions it retained the pigment very intensely, but at other times decolourised into little dots. This latter feature frequently occurred in the case of my bacillus.

Considering the pathogenicity of this organism, capsulated and non-motile in secretions and non-sporing in cultures, with its marked anaërobic gas-producing properties, combined with the appearances of its growth on agar, potato, serum, and in broth, it certainly resembles Welch's bacillus; but, on the other hand, the absence of growth on gelatine or in milk, the indifferent manner in which it reacts to the method of Gram, and the absence of clinical emphysema point rather to the possibility of its being some other allied species. Klein's *B. enteritidis* and the anaërobic bacillus of malignant œdema are, of course, out of the question.

In conclusion it might be added that seventy-two hours after admission the patient's arm was amputated by Mr. Jaffrey, and that complete recovery ensued. My obligation to Dr. Slater for his indispensable help and assistance I should also like to acknowledge here.

[At the conclusion of his paper Dr. Spitta illustrated on the screen by means of photo-micrographs the various points in his paper, showing the organism in the original wound pus, in the secretions of the guinea-pig, and in the cover-glass preparations from the different media which he employed.]

January 21st, 1902.

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19. *The non-absorption of antitoxin from the stomach and rectum.*

By R. T. Hewlett.

Although it seems to be generally accepted by bacteriologists that antitoxin is not absorbed by the mucous membrane of the stomach, I have been able to find few references to this point, and the fact does not seem to be generally known among medical men. Cases treated with antitoxin administered by the mouth are frequently reported in the medical journals, and in a leading article in a recent number of the 'Journal of the American Medical Association' (January 4th, 1902, p. 40) this mode of administration is seriously discussed. As regards the rectum, it might be expected, I think, that antitoxin would be slowly absorbed.

Nicolas and Arloing ('Journ. de Physiologie et Pathologie gén.,' January, 1900, p. 166) were unable to detect any immunity in guinea-pigs produced by the introduction of diphtheria antitoxin into the stomach. Durham, in the last edition of Quain's 'Dictionary of Medicine' (1902), definitely states that antitoxin is completely unabsorbed from either the stomach or rectum.

In order to test these points the following experiments were performed:

1. Two guinea-pigs were fed each with 1000 units of diphtheria antitoxin on April 23rd, and with 2000 units on April 25th. On April 27th one was inoculated with 0·005 c.c., the other with 0·01 c.c. of diphtheria toxin (the minimal lethal dose of which was 0·004 c.c.). The former died in five days, the latter in three days—on the same days as two control animals fed with plain horse serum and receiving the same doses of toxin respectively.

2. A guinea-pig was fed with 1000 units of diphtheria antitoxin on January 27th, 28th, 29th, 30th. On February 1st it was inoculated with 0·01 c.c. of the same toxin used in Experiment 1, and died in two days.

3. A guinea-pig was fed with 1000 units of diphtheria antitoxin on January 29th and 30th. On February 1st it was injected with 0·01 c.c. of diphtheria toxin, and died in three days. (This toxin was controlled on January 27th; 0·01 c.c. killed a guinea-pig in two days.)

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4. A guinea-pig was fed with 5 c.c. of tetanus antitoxin on January 24th, 1 c.c. January 27th, *idem* January 28th, *idem* January 29th. On February 1st it received an acute lethal dose of tetanus toxin and died in two days.

5. A rabbit received *per rectum* diphtheria antitoxin, on January 28th 1 c.c., 29th *idem*, 30th *idem*, 31st 2 c.c. and 2 c.c. (over 2000 units). On February 1st it was injected with 0·12 c.c. of diphtheria toxin (about three lethal doses) and died in two days. A control rabbit, injected with 0·08 c.c. (*i. e.* about two lethal doses), died in two days also.

6. A rabbit received *per rectum* tetanus antitoxin, on January 28th 1 c.c., 29th *idem*, 30th *idem*, 31st 2 c.c. and 2 c.c. On February 1st it and a control animal received a subacute lethal dose of tetanus toxin. Tetanic symptoms were well and equally marked in both animals on February 4th. The control animal ultimately recovered; the one that had received the antitoxin died on February 6th. There was therefore no sign of any protection afforded by the rectal administration of the antitoxin.

7. A guinea-pig received five daily injections of about 0·5 c.c. of diphtheria antitoxin *per rectum* (about 1000 units). A minimal lethal dose of diphtheria toxin killed it on the fourth day.

These experiments show, therefore, that *no trace* of diphtheria or of tetanus antitoxin is absorbed by the mucous membrane of either the stomach or rectum.

I am indebted to Dr. Macfadyen of the Jenner Institute of Preventive Medicine for the antitoxin, and to Dr. Dean of the same Institute for the standardised toxins used in these experiments.

February 4th, 1902.

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20. *An experimental production of the osteo-arthritic type of rheumatoid arthritis.*

By F. J. Poynton and Alexander Paine.

[With Plates VI and VII.]

Upon July 16th, 1901, a man aged 67, who had taken carbolic acid by misadventure, was admitted unconscious to St. Mary's Hospital, and died upon the 18th.

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At the necropsy we found that several of his joints were crippled by a chronic destructive arthritis; this was especially the case with the tarsal joints of the left foot, the left knee-joint, and terminal phalangeal joint of the right index finger. On movement of the knee there was grating. The joint contained two drachms of a clear, glassy, straw-coloured fluid, in which floated a few flakes of exudation. The structures of the articulation were much diseased; the synovial membrane was much thickened, and in places hyperæmic; the cartilage over the outer facet of the patella was completely destroyed, as also in great part that over the articular surfaces of the tibia and femur. Where the cartilages had not been destroyed they had lost their gloss. The bones were eburnated at the points of pressure. The fibrous capsule was moderately thickened, but the changes were essentially within the joint itself.

Lastly, floating in the synovial fluid was a loose body, the size and thickness of a threepenny piece, probably formed by the organisation of inflammatory exudation. The condition was clearly one of non-suppurative, chronic, destructive arthritis. The extensive erosion of the cartilages and the eburnation of the ends of the bones separated it from the group of chronic simple rheumatic arthritis. Neither, in the ordinary sense of the word, was it a gouty joint, for there was no deposit of urates; nor, from the character of the fluid, could it be called a suppurative arthritis. It must therefore be classified among those chronic destructive joint lesions included under the name of rheumatoid arthritis, and among those in that group which we especially associate with later life. The cardiac valves were normal, and there was nothing discovered *post mortem* to show that the patient had suffered from previous attacks of rheumatic fever.

The microscopic and bacteriological investigation.

A few diplococci were found in a film made from the exudation in the knee-joint.

Some pieces of the synovial membrane were fixed in perchloride of mercury, and others incubated in the acid milk medium that we have used for the culture of the diplococcus of rheumatic fever.

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The sections that were cut of the incubated and unincubated synovial membrane showed the presence of diplococci situated especially in the fringes.

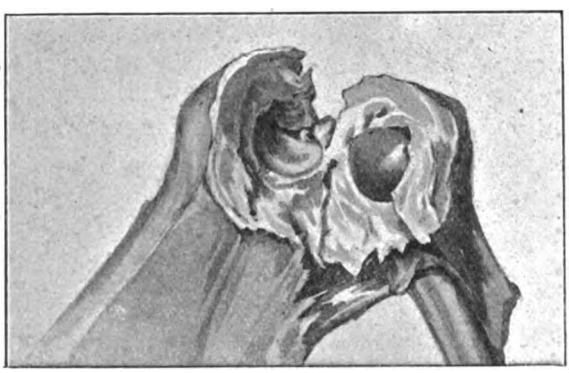
The cultures showed a growth of diplococci and of the *Bacillus coli communis.*

The diplococcus was isolated on blood-agar plates and transferred to blood-agar tubes.

Experimental results.

I. Upon July 24th, 1901, the cultures from two blood-agar tubes were injected intra-venously into a rabbit. Two days

FIG. 18.



The left shoulder-joint of a rabbit, showing rheumatic arthritis (natural size). The figure shows great thickening of the periarticular tissues and joint capsule, the result of an arthritis due to the intra-venous injection of the diplococcus of rheumatic fever. The cartilages of the joint were not affected; the exudation was clear and in considerable amount. The arthritis was of three weeks' duration, and other of the large joints were affected.

afterwards there was arthritis of the left carpus, later arthritis of the left shoulder, and then of both knee-joints. There was no clinical evidence of morbus cordis.

The animal was killed upon August 8th, and a white fluid containing flakes of exudation was found in each of the affected joints. In the films diplococci were demonstrated, and the leucocytes stained well and were not necrotic.

There was no erosion of the cartilages, the heart was not affected, and there were no visceral lesions.

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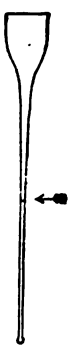
Thus from the first inoculation a severe multiple arthritis had resulted.

II. Upon July 30th another intra-venous inoculation was made into a rabbit.

Throughout September nothing was noticed but some slight wasting of the right hind limb. The first week in October we found a slight excess of fluid in the right knee-joint.

The remarkable feature of this case was the definite atrophy of the muscles of the thigh and leg. At the end of September the limb was practically useless, and the atrophy very obvious. In the second week of October, ten weeks after inoculation, as

FIG. 19.



Pipette containing fluid removed from the right knee-joint of the rabbit referred to in the text. The arrow indicates the upper level of the fluid, which was quite clear. An equal quantity was used for culture purposes, but was found sterile.

there seemed a slight recovery of power in the limb, we killed the animal.

There were no visceral lesions, but the right knee, the only joint affected, contained a slight excess of a clear fluid, part of which was preserved in a sterilised pipette, and part of which was used for inoculation of a culture tube. The right knee-joint was enlarged, and the articular surfaces distinctly though slightly flattened. The edges of the articular surfaces were rounded, and, if compared with the corresponding joint, thickened, giving rise to some lipping. A thickening on the inner condyle of the femur was especially noteworthy.

In two places on the outer condyle of the femur the bone was eroded and the cartilage destroyed.

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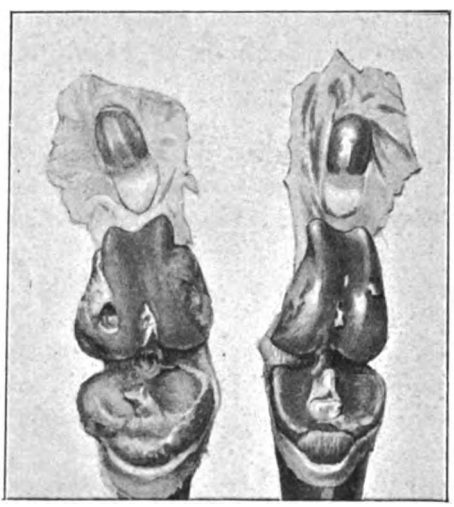
There was both bone formation and bone destruction.

The cartilage on the tibia had lost the natural gloss, and with a lens was seen to be roughened and pitted.

There was also on the outer side of the epiphysial cartilage of the tibia at its posterior limit a small erosion with destruction of cartilage.

The atrophy of the muscles around the joint was very evident;

FIG. 20.



A drawing of the knee-joints (natural size) of the rabbit referred to in the text, which had been inoculated intra-venously with a diplococcus isolated from the knee-joint of a man suffering from chronic rheumatoid arthritis. The left knee-joint is normal. The right knee-joint shows the following changes (the joint capsule was slightly thickened):

1. The articular surface of the femur is thickened, and the cartilage has lost its lustre.
2. The edge of the inner condyle is rounded, and there is a prominence due to a new formation of imperfect bone and cartilage.
3. The edge of the outer condyle is rounded and lipped, and there is an area in which there is destruction of bone and cartilage.
4. The articular surface of the tibia is flattened, the edges are much thickened, and the cartilage has lost the gloss. [The cartilage when the specimen was fresh had a pitted appearance.]
5. At the posterior aspect of the outer facet of the tibia there is a small area where the cartilage was destroyed. [This can hardly be seen in the figure.]
6. The crucial ligaments are swollen and have lost their lustre.

the muscles on the anterior and posterior aspects of both leg and thigh were affected.

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The joint capsule was not greatly thickened, but the ligaments, especially the crucial, were opaque and swollen.

The culture from the joint was sterile.

Thus in this case there resulted from an intra-venous inoculation of a diplococcus, isolated from a case of chronic rheumatoid arthritis, a monarticular arthritis, with excess of clear fluid in the joint cavity, erosion of cartilage and bone, alteration in the shape of the articular surfaces, and marked atrophy of the muscles in the neighbourhood. The injury to the joint was therefore of the nature of an osteo-arthritis rather than a synovitis and capsulitis such as we have observed in the experimental arthritis produced by the diplococcus of rheumatic fever.

The view that some cases of rheumatoid arthritis are of microbic origin has been long maintained, and as early as 1893 Max Schüller described the occurrence of bacilli which exhibited polar staining as present in the joint exudations, and various investigators have contributed to our knowledge of the bacteriology of rheumatoid arthritis.

For example, in this country the researches of Bannatyne, Wohlmann, and Blaxall, published in 1896, are well known. The organism described by them was also a bacillus which was cultivated by Dr. Blaxall.

Chauffard and Raymond, later, in 1896, also isolated a diplobacillus from the synovial fluid and scrapings of the lymphatic glands, but failed to obtain cultivations.

In 1898, von Dungern and Schneider isolated a minute diplococcus from a case of rheumatoid arthritis which had apparently followed rheumatic fever. This diplococcus injected directly into the knee-joint of a rabbit produced changes which they believed to be rheumatoid.

In this investigation of ours it is an interesting point that a monarthritis of this type should have followed an inoculation into the general blood-stream. Whatever the cause or causes of rheumatoid arthritis may be, this appears to be quite certain: that if it is the result of any infection the paths of access are far distant from the joints, and these structures are damaged because they are peculiarly susceptible, and not because there is direct invasion by micro-organisms as in traumatic arthritis, the result of a punctured wound. These sites of infection, whether

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DESCRIPTION OF PLATE VI,

Illustrating Dr. F. J. Poynton's and Dr. Alexander Paine's paper on "An Experimental Production of the Osteo-arthritic Type of Rheumatoid Arthritis." (Page 221.)

A dissection of the hind limbs of the rabbit described in the text. The inner aspect of each limb is represented.

Fig. 1 shows the atrophy of the muscles of the right limb.

Fig. 2 shows the normal size of the corresponding muscles.

From drawings by Danielsson.

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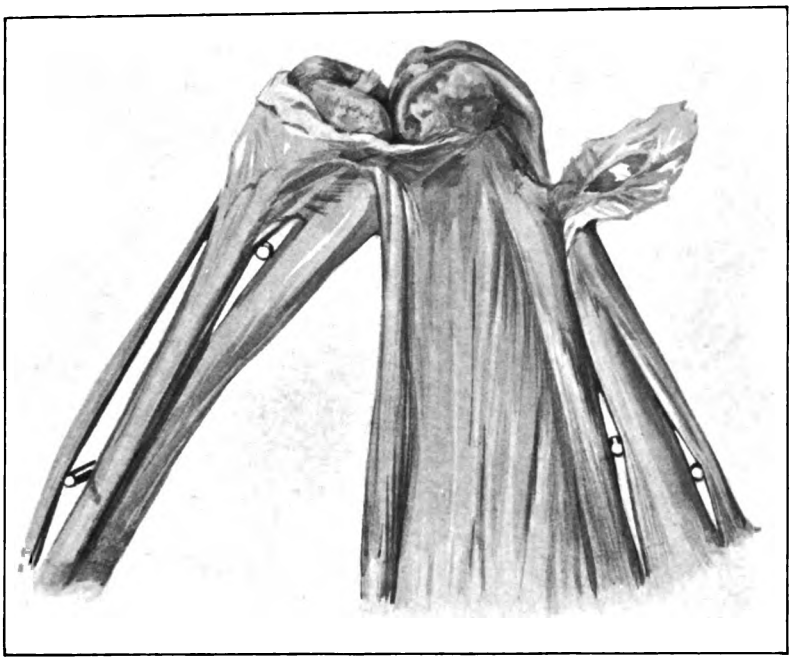

FIG. 1.

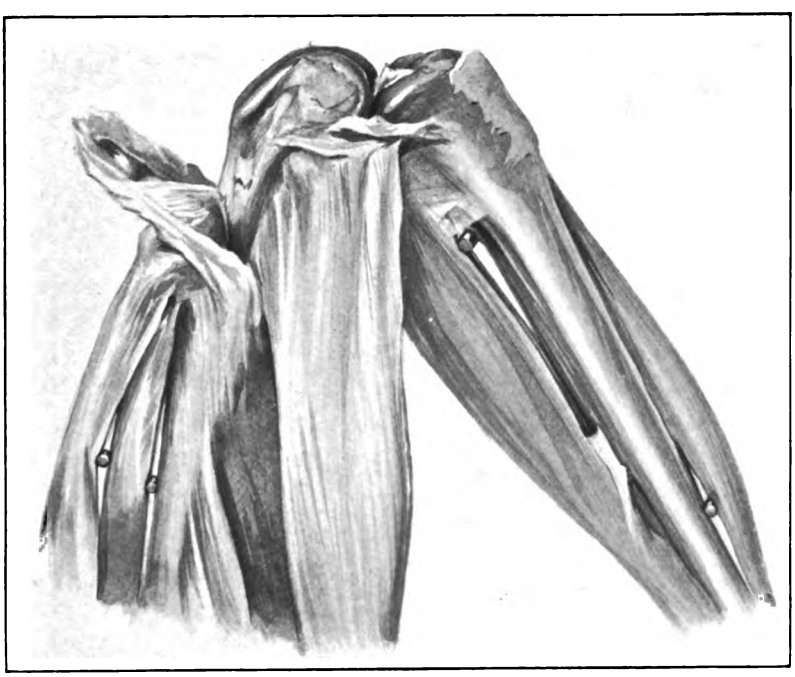

FIG. 2.

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DESCRIPTION OF PLATE VII,

Illustrating Dr. F. J. Poynton's and Dr. Alexander Paine's paper on "An Experimental Production of the Osteo-arthritic Type of Rheumatoid Arthritis." (Page 221.)

FIG. 1.—A section through the synovial membrane taken from the knee-joint of a man aged 67, who suffered from chronic rheumatoid arthritis. Diplococci lie in scanty numbers in the thickened synovial membrane ($\frac{1}{1\,5}$).

FIG. 2.—A section through a fragment of the synovial membrane of the knee-joint of the same patient, the tissue having been first incubated for twenty-four hours in a medium of milk bouillon and lactic acid ($\frac{1}{1\,5}$). Diplococci lie in considerable numbers in the tissue.

FIG. 3.—A section through the synovial membrane of the knee-joint of a girl who died from rheumatic carditis.

The knee had been slightly swollen and tender during life, the condition of the joint being representative of the mild arthritis met with in childhood.

The exudation was clear except for a few flakes; from it the diplococcus was isolated in pure culture.

The figure shows the diplococci lying in the areolar tissue immediately beneath the endothelial lining of the synovial membrane ($\frac{1}{1\,5}$).

The section is represented for comparison with the others; it is from the first case in which the authors succeeded in demonstrating the diplococcus of rheumatic fever in the synovial tissue.

The several figures are from drawings by Danielsson.

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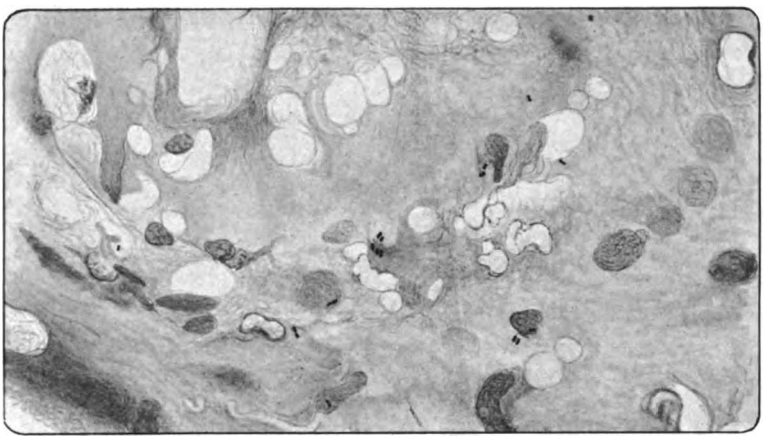

FIG. 1.

FIG. 2.

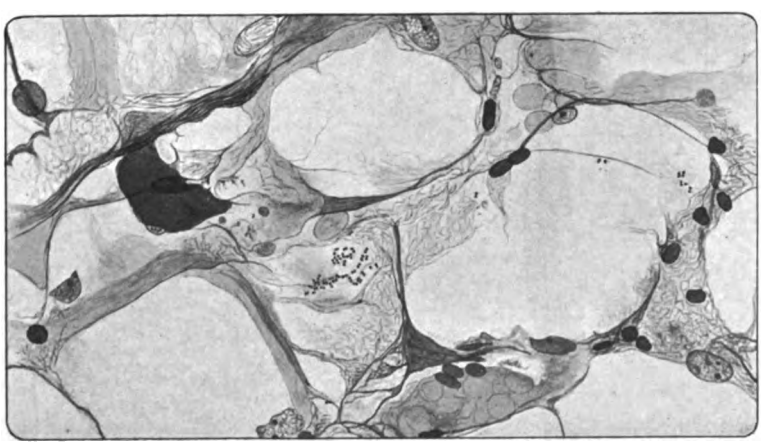

FIG. 3.

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the uterus or the bowel or the throat or elsewhere, in all probability differ in different examples of the disease.

To summarise the conclusions.

1. A diplococcus was present in the synovial membrane of the knee-joint of a man aged 67, several of whose joints showed the chronic destructive changes recognised as occurring in one type of rheumatoid arthritis.

2. This diplococcus was isolated and cultivated in pure growth, both on blood-agar and in a medium of milk and bouillon acidified with lactic acid.

3. Upon two occasions when injected into rabbits it produced a severe arthritis but no cardiac lesion.

4. The organism was isolated from the exudation produced in the joints of the rabbit.

5. In the second instance a monarthritis resulted from the intra-venous inoculation, which showed destruction and formation of bone and cartilage with some flattening and lipping of the articular ends and definite wasting of the muscles in the neighbourhood.

The capsular structures were little affected, and the exudation was clear and sterile.

6. This arthritis differed in type from that which we have hitherto produced with the diplococcus of rheumatic fever.

We conclude, therefore, that—

7. This diplococcus was the cause of the arthritis in the case from which it was isolated, and of the condition produced by experiment in the rabbit.

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January 7th, 1902.

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21. *Low proteid metabolism.*

By Vaughan Harley and Francis Goodbody.

It is well known that different individuals take a very varied amount of food, and it is popularly believed that those large eaters who remain thin do so because a large proportion of the food taken passes through the alimentary tract unaltered. It is our intention this evening to bring forward the case of a fat individual who said she was a very small eater, and still could not keep thin.

The lady was aged 34, and at the time of observation she weighed 72 kilos., her height being 5 feet 7 inches. The previous history of the case showed that she had been very neurotic, and two years ago had suffered from distinct hysterical attacks, with muscular contractions of the arms and legs. She had been greatly bothered with flatulent dyspepsia and chronic constipation. An analysis of the stomach showed a total acidity of 95, volatile acids 13, while the digestive power of the stomach was somewhat delayed, being seven minutes without and five minutes with the addition of hydrochloric acid.

During the time that the observations were made the patient remained entirely in bed, and had massage daily. The diet of each period was subdivided by means of charcoal,—that is to say, charcoal was given at 8 a.m., before the first meal of the day on the first day of analysis, and repeated on the last, the fæces passed between the periods of the two charcoals being collected and representing the refuse during that period. The urine was, of course, collected daily.

Throughout the experiment the quantity of fluid given daily was kept constant, but only that drunk was marked on the charts, as it was impossible to estimate the quantity of moisture in the diet.

During all the periods of analysis it was found that the appearance of the charcoal in the fæces was very greatly delayed—in most cases taking from 60 to 72 hours to make its appearance, while the shortest time was as long as 48 hours. The motions consisted of small, hard, black lumps, with some

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mucus, and in some cases a little fluid round them. During the first period there was on one occasion a trace of blood. A rough analysis of the fæces showed that they contained urobilin, no unaltered bilirubin, and practically no albumen. In consequence of the marked constipation the patient during the first period of seven days passed motions on only five occasions. Microscopically nothing of importance was found in the fæces.

TABLE I.—*Mrs.* ——, *aged* 34, *while taking* 1 *lb. meat daily and* 1200 *c.c. Vichy water. The diet contained* 12·16 *grammes nitrogen and* 25·71 *grammes fat, giving a calory worth of* 7·74 *calories per kilo.*

Date.	Urine.						Fæces.				Absorbed per cent.	
	Wgt.	Qty.	Sp. gr.	N.	U.	U. A.	Qty.	H_2O.	N.	F.	N.	F.
7	72·2	1260	1016	13·23	23·94	0·61	74	73·69	0·75	1·71	96·81	97·49
8	72·0	1500	1017	19·95	36·15	0·91	35	73·69	0·35	0·80	98·47	98·83
9	72·5	1060	1020	13·04	24·17	0·51	53	73·69	0·53	1·22	97·74	98·19
10	71·6	1100	1018	12·65	22·33	0·52	—	65·22	0·44	1·02	98·12	98·52
11	71·1	1080	1016	11·56	21·92	0·52	67	65·22	0·45	1·01	98·12	98·52
12	71·1	1180	1017	12·75	23·95	0·50	—	65·22	0·43	0·95	98·17	98·60
13	70·2	840	1020	11·92	19·99	0·42	63	65·22	0·44	0·96	98·17	98·60
Aver.	71·5	1146	1018	13·51	24·63	0·57	41	68·85	0·48	1·09	97·94	98·39

During the first period the patient took 12·16 grammes of nitrogen and 25·71 grammes of fat. During this period of seven days 1200 c.c. of Vichy water were given daily. Calculating the calories to the weight of the patient, the diet contained 7·74 calories per kilo. As we know, an ordinary individual, under such circumstances, would take from 30 to 40 calories per kilo., while a woman would roughly require 20 to 25 calories per kilo.

In spite of the small diet it was seen that during the first seven days of observation the patient lost only 2 kilos., while during the first six days only 1 kilo. was lost, and, in fact, during the first part of the time she rather increased in weight.

On turning to the urine we find that although the diet contained 12·16 grammes of nitrogen per diem, the average output of nitrogen per diem in the urine was 13·51 grammes, the urea

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being 24·63 grammes and the uric acid 0·57 gramme. We thus see that the patient was passing 1 gramme more nitrogen per diem in the urine than she received in the diet.

For purposes of comparison we might take for example a healthy man of 5 feet 11 inches, who weighed 77·40 kilos. This man, on 1 lb. minced beef, which contained 14·72 grammes of nitrogen and 36·68 grammes of fat—yielding a calory worth of 9·27 calories per kilo.,—lost no less than 2 kilos. in weight, and this loss was a steady fall during the four days of observation. In this case the nitrogen in the urine contained no less than 22·71 grammes, a direct loss to the tissues of 7·99 grammes per diem.

TABLE II.—*Mr.* ——, *aged* 37, *on a diet of* 1 *lb. beef per diem and* 1680 *c.c. of Vichy water. The diet contained* 14·72 *grammes of nitrogen and* 36·68 *grammes of fat, giving a calory worth of* 9·27 *calories per kilo.*

Date.	Urine.						Fæces.				Absorbed per cent.	
	Wgt.	Qty.	Sp. gr.	N.	U.	U. A.	Qty.	H_2O.	N.	F.	N.	F.
16	78·30	850	1028	14·88	29·41	0·64	48	63·15	0·49	2·25	96·67	93·87
17	77·44	1390	1029	25·16	49·07	0·92	—	—	0·50	2·25	96·60	93·87
18	77·29	1760	1027	29·22	55·09	1·02	114	74·02	0·83	2·61	94·36	92·88
19	76·28	1680	1026	21·58	43·51	0·97	—	—	0·83	2·62	94·36	92·88
Aver.	77·40	1420	1028	22·71	44·27	0·89	41	68·59	0·66	2·43	95·50	93·38

During this period of four days this man passed 44·27 grammes of urea and 0·89 gramme of uric acid.

We now come to the analysis of the fæces in these two cases.

In the case of the lady, we have already said that she had considerable constipation, and that there was great delay in the time which it took for charcoal to appear in the motions. The average percentage of water in the fæces was 68·85, the same fact, however, holding good in the case of the man. The average daily output of nitrogen was 0·48 gramme per diem, as compared with 0·66 gramme per diem in a healthy man on a similar diet. The fat in the diet was 1·09 grammes per diem,

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as compared with 2·43 grammes in the case of the normal man. We thus see that the lady absorbed 97·94 per cent. of the nitrogen, while the man, on the same diet, absorbed 95·50 per cent. of nitrogen. In the case of the fat the lady absorbed 98·39 per cent., while the man absorbed 93·38 per cent. of the fat given. However, it is not correct to calculate the absorption by this means, for, as is well known, starving individuals pass a certain amount of fæces, and experiments have shown that, in animals as well as in men, the quantity of nitrogen and fat in the fæces on a purely meat diet is very much the same as that found in starvation.

As the lady kept in such good health on this diet, it was decided to try for a short time what would happen to her metabolism if the diet were diminished to one half. During two periods of five days each she therefore took ½ lb. mutton daily, which contained 6·08 grammes of nitrogen and 12·86 grammes of fat. During the second period we therefore had a diet with a calory worth of 4·15 calories per kilo., the average weight being 66·8 kilos., while during the third period the diet contained 4·16 calories per kilo., her weight averaging 66·5 kilos.

TABLE III.—*Same lady as Table I, on a diet ½ lb. of meat daily and 2100 c.c. of Vichy water. The diet contained 6·08 grammes of nitrogen and 12·86 grammes of fat, giving a calory worth of 4·15 calories per kilo.*

Date.	Urine.						Fæces.				Absorbed per cent.	
	Wgt.	Qty.	Sp. gr.	N.	U.	U. A.	Qty.	H_2O.	N.	F.	N.	F.
2	67·6	1340	1015	8·84	16·17	0·49	95	74·17	0·82	1·11	93·02	96·75
3	66·5	1480	1014	10·47	—	0·57	93	94·40	0·17	0·23	98·55	99·33
4	—	—	—	—	—	—	93	94·40	0·17	0·23	98·55	99·33
5	66·4	640	1014	5·42	9·72	0·31	25	64·61	0·30	0·26	97·44	99·24
6	66·7	1440	1012	8·56	14·40	0·40	53	64·61	0·62	0·85	94·72	97·57
Aver.	66·8	1225	1013	8·32	13·43	0·44	72	78·43	0·41	0·33	96·45	98·43

During these two periods the patient took 2100 c.c. of Vichy water per diem. We see from the tables that the loss in weight

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during the ten days of observation on this very small diet was extremely slight.

TABLE IV.—*Same lady as Tables I and III, on a daily diet of ½ lb. meat and 2100 c.c. Vichy water, containing 6·08 grammes of nitrogen and 12·86 grammes of fat, yielding a calory worth of 4·16 calories per kilo.*

Date.	Urine.						Fæces.				Absorbed per cent.	
	Wgt.	Qty.	Sp. gr.	N.	U.	U. A.	Qty.	H_2O.	N.	F.	N.	F.
7	66·4	1220	1011	6·83	12·78	0·42	80	86·67	0·42	0·45	93·09	96·50
8	66·6	1180	1014	6·34	13·33	0·52	42	86·67	0·22	0·23	96·38	98·21
9	67·1	1660	1011	8·20	15·77	0·51	31	84·13	0·19	0·22	96·88	98·29
10	66·2	1500	1010	6·96	12·19	0·36	32	61·15	0·48	0·51	92·11	96·03
11	66·2	1900	1009	6·27	11·02	0·28	55	61·15	0·83	0·90	86·35	93·77
Aver.	66·5	1492	1011	7·32	13·01	0·42	48	75·95	0·43	0·46	92·96	96·56

An examination of the urine showed that the increase in the quantity of water taken caused only a slight increase in the quantity of urine passed, the quantities being 1225 c.c. and 1492 c.c. respectively.

The nitrogen in the urine during these two periods was 8·32 grammes in the second period, falling to 7·32 grammes during the third period, so that during this period, when taking only ½ lb. meat daily, the patient lost 1 gramme of nitrogen from the tissues per diem.

The urea, during the second and third periods, fell to 13·43 grammes and 13·01 grammes per diem respectively, proportionately the same decrease which we have seen in the nitrogen as compared with Period 1.

The uric acid, on the other hand, only decreased very slightly with the diminution of the diet to one half, as it now stood at 0·44 gramme and 0·42 gramme per diem.

During these two periods the quantity of water in the fæces was 78·03 per cent. and 78·95 per cent., this slight increase being possibly due to the increased quantity of fluids drunk. The fæces contained, on an average, 0·41 and 0·43 gramme of

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nitrogen per diem. The quantity of fat in the fæces during the second period was reduced 0·33 gramme per diem, while during the third period it was only 0·46 gramme per diem. The absorption of proteid and fat was somewhat reduced, being, for nitrogen, 96·45 per cent. as against 92·96 per cent. in the third period, and for fat 98·43 per cent. as against 96·56 per cent. in the third period.

These two series of analyses show how remarkably low the proteid metabolism in this lady must have been in comparison with that in the healthy man; but it must be remembered that women have a much smaller metabolism than men. We will therefore compare the results attained in this lady with those attained in another lady on a somewhat similar diet.

TABLE V.—*Same lady as Tables I, III, and IV, on a mixed diet of* 1 *oz. ham,* 2 *oz. chicken,* 3 *oz. fried sole,* 1 *lb. spinach,* ½ *lb. Brussels sprouts, and* 2100 *c.c. Vichy water daily. The diet contained* 14·69 *grammes of nitrogen,* 19·56 *grammes of fat, and* 131·9 *grammes of carbohydrates, giving a calory worth of* 16·6 *per kilo.*

Date.	Urine.						Fæces.				Absorbed per cent.	
	Wgt.	Qty.	Sp. gr.	N.	U.	U. A.	Qty.	H_2O.	N.	F.	N.	F.
12	66·4	1820	1010	6·18	10·37	0·27	644	88·89	2·05	3·33	86·04	82·97
13	66·2	1300	1011	5·42	9·30	0·27	305	97·53	0·21	0·88	98·57	95·50
14	66·2	1840	1010	8·09	13·83	0·73	256	92·56	0·55	1·14	96·26	94·17
15	66·7	1220	1012	7·09	12·20	0·68	180	97·27	0·66	2·11	95·51	89·11
Aver.	66·4	1545	1011	6·69	11·42	0·48	346	91·57	0·87	1·87	94·07	90·44

During this period the lady took a diet consisting of 1 oz. ham, 2 oz. chicken (boiled or roast), 3 oz. fried sole, 1 lb. spinach, ½ lb. Brussels sprouts, no butter. This diet contained 14·69 grammes of nitrogen, 19·56 grammes of fat, and 131·9 grammes of carbohydrates, while 2100 c.c. of Vichy water was drunk per diem. During this period the average weight was 66·4 kilos., so that she took 16·6 calories per kilo. per diem. During the four days on which she was on this small diet her

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weight increased from 66·4 kilos. to 66·7 kilos. During this period the quantity of urine increased to 1545 c.c., while the quantity of nitrogen excreted per diem fell to an average of 6·69 grammes.

We thus see, on comparing this nitrogen output on a mixed diet with that on a purely meat diet, that although the diet contained double the quantity of proteid there was a diminution in the nitrogen output, owing to the sparing influence of the fat and carbohydrates in the diet on the metabolism.

The urea was correspondingly low, the average being 11·42 grammes per diem, while the quantity of uric acid daily excreted remained practically unaltered, 0·48 gramme.

The mixed diet had a marked influence on the fæces, the quantity passed being increased to no less than 346 grammes per diem. There was also an increase to be noticed in the quantity of water in the fæces, as they now contained 91·57 per cent. The fæces during the period of mixed diet contained, on an average, 0·87 gramme of nitrogen, almost double the amount found on the purely meat diet. The fat in the fæces increased slightly to 1·87 grammes per diem. In consequence of the composition of the fæces being thus altered, we have now an absorption of proteid of no less than 94·07 per cent., while the absorption of fat was 90·44 per cent.

TABLE VI.—*Miss* ——, *aged* 41, *while taking* 40 *oz. milk,* 2 *oz. meat,* 2 *oz. bird,* 2 *oz. fish,* 4 *oz. greens,* ½ *oz. butter, and nine biscuits. The diet contained* 16·24 *grammes of nitrogen,* 67·69 *grammes of fat, and* 88·69 *grammes of carbohydrates, yielding a calory worth of* 22·91 *per kilo.*

Date.	Urine.						Fæces.				Absorbed per cent.	
	Wgt.	Qty.	Sp. gr.	N.	U.	U. A.	Qty.	H_2O.	N.	F.	N.	F.
13	60·43	1820	1012	16·93	28·03	0·65	110	77·34	1·15	2·83	91·64	95·82
14	60·52	1830	1012	14·09	24·52	0·59	110	77·34	1·15	2·83	91·64	95·82
15	60·07	1710	1015	15·39	30·10	0·80	117	84·91	0·81	2·00	95·01	97·05
16	60·52	2090	1014	16·51	30·73	0·79	151	86·35	0·92	2·33	94·34	96·56
Aver.	60·39	1863	1013	15·73	28·35	0·71	122	81·49	1·01	2·50	93·16	96·31

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We can now compare this with the case of another lady, who weighed 60 kilos., and who, during the time of analysis, took a diet consisting of 40 oz. milk, 2 oz. meat, 2 oz. bird, 2 oz. fish, 4 oz. greens, ½ oz. butter, and nine biscuits. She was habitually a small eater, and this diet contained only 16·24 grammes of nitrogen per diem, 67·69 grammes of fat, and 66·69 grammes of carbohydrates. The average quantity of fluid taken per diem during this period was 1960 c.c. In consequence of the fat in the diet being so much larger than in the former case, in spite of the carbohydrates being nearly half the original weight, the calory worth of this diet was no less than 22·91 calories per kilo. During this period the lady passed, on an average, 1863 c.c. of urine per diem, corresponding pretty nearly with the quantities previously recorded, while the quantity of nitrogen in the urine, on the other hand, was 15·73 grammes per diem.

The weight during this period of four days remained practically constant, and the nitrogen in the urine, added to that passed in the fæces, equalled the quantity taken in the diet, so that we can consider that during this period the case was on nitrogenous equilibrium.

The urea during this period was 28·35 grammes, and the uric acid 0·71 gramme.

During this period the first charcoal took twenty-nine hours to appear, while the second charcoal took twenty-two hours, and since the bowels acted once daily, it may be said that there was no constipation. An average of 81·49 per cent. of water was found in the fæces per diem. The quantity of nitrogen in the fæces was 1·01 grammes, while the fat was 2·50 grammes per diem. The absorption of nitrogen was therefore 93·16 per cent., while the absorption of fat was 96·31 per cent.

These two cases compare very favourably, and bring out very markedly the idiosyncrasies of individuals with regard to metabolism, and the fatness of the first lady can hardly be put down to greed. *March 4th*, 1902.

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22. *The nitrogenous metabolism in a case of Bright's disease.*

By J. A. Butler and H. S. French.

From the Physiological Laboratory, Guy's Hospital.

As far as we have been able to discover, the only published experiments upon the nitrogenous metabolism in Bright's disease have been continuous for but short periods. The longest we have found is of twelve days' duration, upon a man aged 47, with chronic interstitial nephritis, by Prior (50) in 1891. The uric acid, the total urinary nitrogen, and the fæces nitrogen were estimated; the food nitrogen was sometimes estimated and sometimes calculated from diet tables, whilst the urea was not estimated at all. Upon two other occasions Prior (50) estimated the uric acid, the albumen, the urea, the total urinary nitrogen and the fæces nitrogen, but each investigation lasted seven days only. P. Müller (45), Van Noorden and Ritter (64), Mann (41), Kornblum (32), and Baginsky (3A) all publish researches extending over periods of a few days. In all the total nitrogen output was determined, but in many the nitrogen in the food was wholly or partly taken from diet tables, and in none was the urea determined. Korkounov (31), Evdokimov (13), Garine (16), and Grigoriev (18) have published researches upon the subject, but their papers, which are in Russian, are not easily accessible, and we have not been able to obtain full particulars of their work.

The case we have investigated was one of subacute parenchymatous nephritis in a boy aged 7, under the care of Dr. Taylor and Dr. Fawcett, in John Ward, Guy's Hospital. The research was continuous for forty-one days, and included a period of mild uræmia. The estimations carried out daily were—(1) the total nitrogen in the urine; (2) the urea; (3) the uric acid; (4) the coagulable proteid; (5) the total nitrogen in the fæces; (6) the nitrogen in the milk supply. From time to time additional estimations were necessary, as other articles of food were added to his diet.

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No attempt was made to estimate the nitrogen loss by the skin, because we felt that any method of doing so that we could devise must be too inaccurate to correspond with the accuracy we hoped to attain in our other work. The boy was suffering from psoriasis, which may have made the skin loss more than usual.

We have divided the report of our work into the following sections:

I. A clinical account of the case.
II. The methods we have used.
III. The detailed tables of our results.
IV. The urea.
V. The uric acid.
VI. The coagulable proteid.
VII. The "other bodies."
VIII. The fæces.
IX. The unrecovered nitrogen.
X. General conclusions.
XI. References.

Section I.

A clinical account of the case.

W. W—, male aged 7 years, was admitted under the care of Dr. Fawcett, January 10th, 1901, for cough, dropsy, and albuminuria. He was the eighth child of a family of twelve, of whom only two besides the patient were living.

There was a history of varicella three years previously, and of attacks of psoriasis. There was no history of diphtheria or scarlet fever. His present illness began about October, 1900, and was attributed by his mother to getting his feet wet. His feet began to swell about December 10th, and his eyelids and face were swollen about December 27th. No history of hæmaturia could be obtained.

On admission (January 10th) his pulse was 112, respirations 40 per minute, and temperature 100·4° F. He had a good deal of bronchitis and general œdema. The cardiac sounds were normal, and the pulse tension was not particularly high.

The urine had a sp. gr. of 1040, and contained about 12 parts

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per 1000 of albumen (by Esbach). There was a large deposit of urates.

He had numerous patches of psoriasis on the extensor surfaces of his arms and legs, and some on the trunk. He was very drowsy, and during the first two or three days in the ward he slept much, and passed little urine.

Under treatment his condition improved, and on January 17th he was passing much more urine, and had very little œdema. After this his condition varied considerably. The albumen never disappeared from the urine, and on several occasions as large a proportion as 14 parts per 1000 (by Esbach) was recorded. Granular and epithelial casts were found.

The research began on February 19th. For some days previously his diet had been milk only. He had slight œdema of the feet and legs. The abdomen was large, but there was no ascites. He had no bronchitis. The cardiac sounds were normal. There were numerous patches of psoriasis on the legs, arms, and trunk, the face and scalp being free. He had a hot bath every night, and was taking the following drugs:

1. ℞ Ferri et Ammonii Citratis . . gr. vj.
   Liquoris Arsenicalis . . ♏iv.
   Liquoris Ammonii Acetatis . ʒj.
   Potassii Citratis . . . gr. x.
   Syrupi Aurantii . . . ʒss.
   Aquam ad . . . . ℥j.
   The mixture given three times a day.
2. ℞ Pulveris Scammonii Compositi (B.P.) gr. x.
   The powder given in a cachet once a day.

February 19th.—Bowels opened (= B.O.) 1.

20th.—B.O. 2.

21st.—B.O. 6.

22nd.—The Mixture 1 was omitted, and the following given for the rest of the time:

3. ℞ Potassii Citratis . . . gr. xx.
   Aquam Menthæ Piperitæ (B.P.) ad ʒj.
   The mixture given three times a day.

23rd.—The Powder 2 was not given to-day. B.O. 4.

24th.—B.O. 2.

25th.—The patient vomited a very small amount of clear watery fluid. B.O. 4.

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27th.—B.O. 5.

28th.—The patient was drowsy. He slept about one and a half hours during the daytime. The Powder 2 was again omitted. B.O. 1.

March 1st.—A few patches of psoriasis appeared on the face, and fresh patches on the trunk. B.O. 2.

2nd.—The Powder 2 was reduced by one half, and from this date he took 5 grains each night, in a cachet unless otherwise stated. He vomited again to-day a very small quantity of clear fluid of acid reaction. Those who saw him agreed that he had become distinctly uræmic; it is not easy to bring this out clearly in a short report, as the change was gradual; but the amount of urine passed fell markedly, and he took food very badly.

3rd.—He was very drowsy, and slept about three hours in the daytime. He complained of headache and of feeling sick. He took food badly. B.O. 1.

4th.—He vomited three times, all the vomits being quite small. There was slight œdema of the face. He slept about one and a half hours during the morning, and took little food all day. B.O. 5.

5th.—He vomited once. Some œdema of face.

6th.—Œdema of face less. Patient was brighter. He vomited once, but took his food a little better. B.O. 2.

7th.—Patient complained of headache; his psoriasis was getting worse. The hot baths were discontinued from this date. He vomited once. B.O. 2.

8th.—The œdema of legs and feet was getting worse. There was also slight œdema of the face. B.O. 1.

9th.—Patient complained of headache and feeling sick. B.O. 6.

10th.—Patient vomited once, and took his food very badly. There was a great deal of swelling on both sides of the face, over the parotid glands.

11th.—The parotid swelling was less marked, and he took food better. The powder was not given. B.O. 4.

12th.—Much general œdema, and abdomen larger. He complained of headache, vomited slightly twice, and during the night passed urine into the bed in his sleep. He took little food. B.O. 2.

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13th.—Œdema less. He vomited once.

14th.—Fair amount of general œdema. Face less œdematous; abdomen very large. He complained of slight headache. He began taking his food better, and from his general condition it was agreed that the uræmic symptoms had markedly abated.

15th.—Headache. Œdema of face slight, but marked in feet and legs. He took his food well. B.O. 3.

16th.—Headache and feeling of sickness. Marked œdema of legs and feet. A fine red papular rash appeared on the shoulders, and caused irritation and itching.

17th.—Rash more marked. Vomited once. B.O. 4.

18th.—Patient was brighter and more cheerful, complained of irritation from the rash; was taking his food well.

19th.—Slept for one hour during morning. Some œdema of face. B.O. 2.

20th.—Rash still present, but it caused less irritation. A good deal of œdema of the face, loins, legs, and feet. B.O. 1.

21st.—Œdema about the same. Psoriasis getting better and rash disappearing. B.O. 4.

22nd.—Œdema about the same. B.O. 4.

23rd.—Œdema slightly less; both the rash and the psoriasis were disappearing. B.O. 5. Patient did not sleep well during the night, but took his food very well.

24th.—Œdema of feet, legs, and loins persisted; abdomen very large, but no ascites found. The powder was not given. B.O. 3.

25th.—Patient vomited slightly once, but continued to take food well. B.O. 3.

26th.—Patient was drowsy this morning. There was some œdema of the face and eyelids. The powders were discontinued from to-day. B.O. 1.

27th.—Œdema less. Patient brighter. B.O. 1.

28th.—Only slight œdema of the feet and legs. Psoriasis almost gone. Rash quite gone. B.O. 1.

29th.—B.O. 1.

30th.—Some headache in the afternoon. Patient was not quite so well, and took less food. B.O. 2.

31st.—Patient complained of headache, was drowsy, and less well. He took less food, and seemed to be entering upon a second attack of uræmia.

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April 1st.—End of period of observation. As nearly as could be judged there was about the same amount of œdema of the feet and legs as at first. Œdema of legs and feet was present all through, but has not been noted every day. Although the abdomen became very large at times, there was never any definite ascites, nor were there any signs of fluid in the chest.

The vomits recorded have always been very small, on no occasion more than about 30 c.c., and generally much less.

The temperature was taken *per rectum* every four hours throughout; at the same times the pulse and respirations were counted. The highest temperature recorded was 99·4°. This was reached on six occasions, namely:

March 24th.	2 p.m.	Pulse 100	Respiration 30
„ 25th.	6 p.m.	„ 104	„ 30
„ 28th.	6 p.m.	„ 96	„ 34
„ 29th.	6 p.m.	„ 104	„ 30
„ 30th.	6 p.m.	„ 96	„ 28
„ 31st.	6 p.m.	„ 100	„ 28

The lowest temperature recorded was 96°, on March 16th, at 2 a.m., when pulse = 66, respiration = 15.

Except where otherwise stated, the patient slept well throughout the night (ten to eleven hours). He took no exercise during the period he was under observation, and except on a few occasions, when he was allowed to sit up for an hour or two, wrapped in a blanket, he was kept in bed the whole time. He never had any hæmaturia.

Section II.

The methods we used.

1. *Supervision of the patient.*—The patient was under the charge of two special nurses, of whom one or other was always in attendance day and night. Each period of twenty-four hours began at 9 a.m.

2. *Administration and measurement of the food.*—(*a*) *Milk.*—This formed the major part of the diet throughout. The day's supply (2000 c.c.) was measured out[1] at 9 a.m. with a litre flask, and stored in a clean dry Winchester quart stoppered

[1] By one of us.

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bottle. A sample of the same milk was taken for analysis each day. The milk required by the patient from time to time was taken by the nurse from the quantity measured out, any portion unconsumed being at once returned to the bottle. A special drinking vessel was used, which was washed only at the end of each day. The quantity remaining in the Winchester quart at 9 a.m. of the next day was drained[1] into a graduated cylinder, and the amount read off. This, deducted from the amount measured out, gave the milk consumed.

The following articles were subsequently added to his diet:

(*b*) *Bread.*—A quantity, free from crust, was placed in a closely covered tin, and the tin and bread weighed together.[1] The bread eaten by the patient was taken by the nurse from this tin, and the remainder, with the tin, was weighed[1] at the end of each day. The difference between the two weighings gave the amount consumed by the patient. A sample of the same bread was taken for analysis.

(*c*) *Biscuit.*—The dinner biscuits were small and dry, and were weighed in the same manner as the bread. A sample was analysed.

The Garibaldi biscuits were found to vary extremely little in weight. The following are the weights:

(α) Of sixteen biscuits together . . = 327·70 grammes.
From which the average of each biscuit = 20·48 „

(β) Of single biscuits, taken at random:

(i) = 20·50 grammes.
(ii) = 20·30 „
(iii) = 20·40 „
(iv) = 20·53 „

The number of these biscuits consumed each day was counted, and this, multiplied by the average weight of a single biscuit, gave the quantity consumed. A sample was taken for analysis.

(*d*) *Liebig's extract of meat.*—A sample having been taken for analysis, the remainder was weighed in the containing jar. It was kept closely covered; a spoonful or more was taken by the nurse as required, and, to ensure that it all reached the patient, it was stirred into boiling water with the same spoon until dissolved. The jar with its contents was weighed[1] each day, the successive differences giving the daily consumption.

[1] By one of us.

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(*e*) *Other articles.*—The drugs given to the patient are mentioned in the clinical account. The amount of nitrogen they contained was calculated to be so small that we thought it might be neglected.

Water, both plain and aërated, was supplied to the patient when he asked for it; the quantity was only roughly measured by the nurse in fluid ounces.

He was also allowed a few sweets (acid drops) during a portion of the time. The nitrogen in these was practically *nil.*

3. *The collection and measurement of the urine, fæces, and vomits.* —(*a*) *The urine.*—Previous to the beginning of the research, the patient was trained by his nurses not to defæcate without having previously passed all his urine. Fæces and urine were thus collected quite separately. A special vessel, washed only at the end of each day, was kept for his use; after each micturition the nurse poured the urine into a clean stoppered Winchester quart bottle reserved for that day's urine. At 9 a.m., the end of each day, the bottle containing the whole quantity collected during the previous twenty-four hours was handed over to us.

The amount was measured[1] in a graduated cylinder, to the nearest c.c., and a sufficient quantity of the mixed urine taken for the different analyses.

The reaction to litmus-paper was recorded,[1] and the specific gravity read off on a urinometer. For the last thirty-one days the specific gravity was also ascertained by weighing a measured volume (*vide* albumen estimation).

(*b*) *The fæces.*—Each motion was passed into a separate porringer, and as many of these as had been used were handed over to us at the end of each twenty-four hours. The contents of the whole number were washed with a jet of distilled water into a large weighed evaporating basin and well mixed with a glass rod, hydrochloric acid being added until they distinctly reddened litmus-paper. They were then put into a hot-water oven and kept at about 80° C., being stirred from time to time until they appeared dry; this took from twelve to thirty-six hours, after which they were further dried for about six hours in a hot-air oven between 100° C. and 110° C. They were allowed to cool in a desiccator over strong sulphuric acid, and then weighed in the evaporating basin to the nearest decigramme.

[1] By one of us.

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The dried fæces were powdered as finely as possible in a mortar, and a sample kept for analysis.

(*c*) *The vomits.*—These were collected separately in porringers. All were extremely small. Analysed separately at first, they were found to contain so little nitrogen that subsequent vomits were mixed with the fæces and estimated with them. Further mention of this is made in Section VIII.

4. *The methods of analysis.*—The pipettes and burettes used were carefully standardised before the experimental work began. Several blank Kjeldahl estimations were made to determine the correction for the apparatus.

The Kjeldahl method, as described by Kossel (33), was employed for the estimation of the total nitrogen in the milk, bread, Garibaldi biscuit, dinner biscuit, Liebig, urine, and fæces. Two estimations of the milk, urine, and fæces were made each day. The results of the analyses of the foodstuffs are given in Table II.

The urea was estimated by the Mörner-Sjöquist (44) process, in two 5 c.c. samples each day.

The uric acid was determined by Hopkins' (26) potassium permanganate method, in two 100 c.c. samples each day.

The albumen was estimated by the trichloracetic acid method from February 20th to 28th inclusive, for the remainder of the time by a heat coagulation process. The following are detailed descriptions of each:

(*a*) *The trichloracetic acid method.*—To two 50 c.c. samples of urine each day an equal quantity of 10 per cent. trichloracetic acid was added. After standing, the precipitate was filtered off and washed with a jet of hot 5 per cent. trichloracetic acid, until the washings gave no reaction with sodium hypobromite. The filter-paper with the precipitate was dried, first on a water-bath below 60° C., until apparently dry; then in a hot-air oven at 90° C. to 120° C. for four hours; and finally in a desiccator over strong sulphuric acid for four days. It was then weighed, and the known weight of the dry filter-paper deducted. The percentage of nitrogen in four samples of the precipitated albumen was determined by Kjeldahl, and from this the nitrogen as albumen in each day's urine calculated.

(*b*) *The heat coagulation process.*—Fifty c.c. of urine were run into an india-rubber corked flask, the weight of the cork and

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a day		The nitrogen balance.			The uric acid relation.		The urea nitrogen relations.		
Nitrogen as coagulable proteid in urine.	Nitrogen as "other bodies" in urine.	Daily nitrogen balance.*	The progressive nitrogen deficit.	Patient's weight each day without clothes.	The ratio. Uric acid nitrogen to total nitrogen in urine.	The ratio. Uric acid as such to urea as such.	The total nitrogen in the urine being regarded as 100, the urea nitrogen equals—	The total nitrogen in the urine, *minus* the coagulable proteid nitrogen, being regarded as 100, the urea nitrogen equals—	
[2·0706]		−1·4621	1·4621	21·15 kg.	1 : 260	1 : 134	72·125	—	
0·6910	1·8995	−0·4091	1·8712	21·03 „	1 : 161	1 : 79	68·846	74·951	
0·9321	0·4537	−0·5087	2·3799	21·15 „	1 : 168	1 : 98	82·029	92·885	
0·8100	1·2775	−0·3438	2·7237	21·03 „	1 : 178	1 : 92	72·230	80·758	
0·9405	0·7697	−1·9761	4·6998	—	1 : 115	1 : 63	77·193	87·783	
0·6601	0·2730	+0·9604	3·7394	21·03 „	1 : 86	1 : 53	86·056	94·608	
0·4804	0·7983	−0·1665	3·9059	—	1 : 61	1 : 33	75·354	82·484	
0·5894	1·2126	−0·7527	4·6586	21·09 „	1 : 98	1 : 46	72·910	79·679	
0·6944	1·3285	−0·3501	5·0087	20·81 „	1 : 103	1 : 52	70·600	78·235	
0·6128	0·8641	−3·0639	8·0726	20·52 „	1 : 89	1 : 49	76·517	84·344	
1·1890	0·8469	+0·4890	7·5836	20·75 „	1 : 138	1 : 71	72·494	85·937	
1·1578	0·9957	+0·1755	7·4081	20·81 kg.	1 : 87	1 : 45	71·971	84·126	Uræmic period.
0·8916	0·7779	+1·5316	5·8765	21·03 „	1 : 71	1 : 36	72·080	83·964	
0·2085	0·5997	+2·4575	3·4190	21·03 „	1 : 69	1 : 37	75·760	80·494	
0·5151	0·6142	+0·5093	2·9097	20·98 „	1 : 66	1 : 37	77·141	85·467	
[1·6026]		−0·8287	3·7384	21·09 „	1 : 68	1 : 36	74·255	—	
0·3808	0·9712	−0·6287	4·3671	20·75 „	1 : 74	1 : 37	70·244	76·351	
0·5956	0·8392	+0·2916	4·0755	20·41 „	1 : 72	1 : 37	71·692	80·712	
0·6208	0·7865	+1·3569	2·7186	—	1 : 66	1 : 35	74·036	82·988	
0·6232	0·5506	+0·6130	2·1056	21·83 „	1 : 80	1 : 41	71·530	83·619	
0·5189	1·0631	−2·4127	4·5183	21·66 „	1 : 90	1 : 43	67·349	75·118	
0·6104	0·5251	+2·0342	2·4841	22·62 „	1 : 70	1 : 35	70·977	83·334	
0·5705	0·6281	−2·7450	5·2291	22·00 „	1 : 72	1 : 38	74·928	84·442	
0·3814	0·7050	−1·3729	6·6020	22·34 kg.	1 : 87	1 : 49	79·630	85·390	
0·6373	0·6210	−1·0128	7·6148	22·23 „	1 : 107	1 : 60	77·940	87·280	
0·5169	0·7630	−2·7370	10·3518	22·45 „	1 : 120	1 : 64	74·275	82·576	
0·8693	0·8189	+0·0672	10·2846	—	1 : 98	1 : 53	75·641	85·975	
0·7134	0·8093	−2·0080	12·2926	22·85 „	1 : 129	1 : 71	76·907	85·888	
0·6785	0·3345	+0·1527	12·1399	—	1 : 110	1 : 67	85·269	93·966	
0·3108	1·9459	−1·2674	13·4073	22·13 „	1 : 146	1 : 74	70·931	73·815	
0·2042	2·0909	+1·0517	12·3556	23·19 „	1 : 115	1 : 58	69·960	71·825	
0·9792	0·8703	−0·6019	12·9575	23·59 „	1 : 204	1 : 111	76·561	87·150	
0·6642	0·9449	−2·0034	14·9613	23·63 „	1 : 74	1 : 41	77·375	84·822	
0·7254	1·1018	−2·5232	17·4845	24·10 „	1 : 72	1 : 40	76·765	84·056	
0·5010	1·2126	−0·1382	17·6227	24·55 „	1 : 60	1 : 34	80·449	84·887	
0·8355	0·9205	−2·7033	20·3360	24·38 „	1 : 64	1 : 36	79·045	87·086	
0·7812	1·0244	−0·8580	21·1940	23·93 „	1 : 65	1 : 37	81·037	87·642	
0·6522	2·3484	−1·1868	22·3808	23·13 „	1 : 72	1 : 36	69·115	73·850	
0·3957	1·0304	−1·3754	23·7562	22·68 „	1 : 81	1 : 48	83·957	87·552	
0·6306	0·9839	+2·0378	21·7184	21·94 „	1 : 72	1 : 41	80·139	86·374	
0·5510	0·9934	+0·9606	20·7578	21·20 „	1 : 59	1 : 31	74·539	81·440	
26·7990	39·7891	—	20·7578	—	—	—	—	—	
0·6536	0·9706	−0·5063	—	—	1 : 88	1 : 48	75·637	83·438	

Uræmic period.

*trogen in urine and fæces.

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e amount of food taken daily and the percentage nitrogen in it.

Per cent. nitrogen in bread.	Average weight of each biscuit 20·48 grms. Garibaldi biscuits.	Per cent. nitrogen in Garibaldi biscuits.	Weight of Liebig.	Per cent. nitrogen in Liebig.	Weight of dinner biscuits.	Per cent. nitrogen in dinner biscuits.	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
1·2907	—	—	—	—	—	—	
1·2907	—	—	—	—	—	—	
1·2907	—	—	—	—	—	—	
1·2907	—	—	—	—	—	—	
1·2907	12 biscuits	1·0000	—	—	—	—	
—	4 „	1·0000	—	—	—	—	
—	11 „	1·0000	—	—	—	—	
—	3 „	1·0000	—	—	—	—	
—	3 „	1·0000	—	—	—	—	
—	6 biscuits	1·0000	—	—	—	—	
—	3 „	1·0000	—	—	—	—	
—	3 „	1·0000	—	—	—	—	
—	1 biscuit	1·0000	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	15·104 grms.	9·4206	68·73 grms.	1·5921	
—	—	—	27·677 „	9·4206	73·62 „	1·5921	
—	—	—	16·154 „	9·4206	80·65 „	1·5921	
—	—	—	17·349 „	9·4206	89·55 „	1·5921	
—	—	—	21·352 „	9·4206	67·12 „	1·5921	
—	—	—	16·622 „	9·4206	81·60 „	1·5921	
—	—	—	13·307 „	8·8214	86·05 „	1·5921	
—	—	—	6·591 „	8·8214	62·74 „	1·5921	
—	—	—	8·013 „	8·8214	42·70 „	1·5921	

Uræmic period.

s of nitrogen as different foodstuffs, at different periods of the investigation, were as follows:

As milk.	As bread.	As Garibaldi biscuit.	As Liebig.	As dinner biscuit.
0 per cent.	—	—	—	—
25 „	23·75 per cent.	—	—	—
2 „	—	14·88 per cent.	—	—
0 „	—	—	—	—
9 „	—	—	13·29 per cent.	10·52 per cent.

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flask being known. The urine, cork, and flask were weighed; the difference gave the weight of urine taken, and also its accurate specific gravity. The urine was then boiled, and, while boiling, 5 per cent. acetic acid was added from a burette until no further coagulation occurred. About 5 c.c. was usually added in this way. The flask was corked, allowed to cool, and again weighed.

The coagulated proteid was then removed by filtering, and the filtrate tested with nitric acid to be sure that none remained. The nitrogen in two 10 c.c. samples of the proteid-free urine was estimated by Kjeldahl.

But 10 c.c. of this boiled urine = 10 c.c. of the original urine $\times \frac{\text{weight after boiling}}{\text{weight before boiling}}$. Therefore the nitrogen found in 10 c.c. of boiled urine was multiplied by the factor $\frac{\text{weight before boiling}}{\text{weight after boiling}}$, to give the nitrogen in 10 c.c. of original urine freed from coagulable proteid. The total nitrogen in the urine being known, the difference between this and the nitrogen in the proteid-free urine gave the coagulable proteid nitrogen.

The greatest correction was—

$$\frac{50{\cdot}462 \text{ (weight in grammes before boiling)}}{56{\cdot}043 \text{ (weight in grammes after boiling)}};$$

usually it was much less.

Section III.

Tables of results.

Tables I and II give *in extenso* our experimental results and calculations from them. They are referred to in the different sections, and summaries are there made. The meaning of the figures is explained by the headings of the columns.

The following are the notes we wish to make about these two tables:

1. When not otherwise specified, two estimations were made in every case, and the mean taken. Whenever, in the following notes, it is stated that the higher of the two values was taken, this was because the difference between the two observations was more than 1 per cent. from the mean.

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2. *The volume of urine.*—The figures are for urine actually measured, except on—

March 9th, when 285 c.c. was measured, and nurse reported ℥j (= 28 c.c.) spilled.

March 12th, when 267 c.c. was measured, and nurse reported ℥iij (= 85 c.c.) passed into bed.

March 25th, when 1490 c.c. was measured, and nurse reported ʒij (= 7 c.c.) spilled.

March 26th, nurse reported a small quantity spilled, for which we made no allowance.

3. *The specific gravity of the urine.*—When no decimal place is given, there was a urinometer reading only. Otherwise the figure is calculated from the weight of a measured volume.

4. *The milk.*—March 3rd, nurse reported a small quantity spilled. We did not correct for this, so that it was calculated as having been taken by the patient.

One estimation only: February 19th, March 3rd, March 21st.

The higher value taken: March 19th.

5. *The vomits.*—All were extremely small. They were lost on February 25th (1), February 28th (1), March 3rd (3). They were separately estimated, and the nitrogen added to the fæces on the following days:

March 5th . .	=	0·0483 gramme nitrogen.
March 6th . .	=	0·0406 „
March 14th . .	=	0·0629 „

They were estimated along with the fæces on March 10th, 12th, 17th, and 24th.

6. *The fæces.*—On March 3rd the amount was so small one Kjeldahl only was made. There were three estimations February 20th, 22nd, and 23rd.

7. *Total nitrogen in urine.*—One estimation only on March 4th and 7th.

Higher value taken on March 3rd and 21st.

8. *Urea nitrogen.*—One estimation only on February 25th, 26th, and 28th; March 6th, 7th, 12th, 22nd, and 29th.

Higher value taken on March 2nd, 5th, 11th, and 28th.

9. *Uric acid nitrogen.*—One estimation only on March 4th.

Higher value taken on February 21st, March 1st, 2nd, 12th, 19th, and 22nd.

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10. *Proteid-free urine.*—No estimation at all on February 19th and March 6th.

Higher value taken on March 9th, 10th, 21st, and 25th.

The columns of the tables are arranged so as to correspond: the urine and fæces figures, for example, are for the day on which the patient passed the urine and fæces; the milk figures for the day on which he consumed the milk.

The total intake and the total output nitrogen for each day, the progressive nitrogen deficit, and the patient's weight for each day are represented graphically in the chart.

Section IV.

The urea.

In text-books of medicine (11) the statement is often met with that in Bright's disease, and particularly in uræmia, the urea is diminished. Authors do not specify whether this diminution is relative as well as absolute.

That the absolute quantity of urea excreted by a person with uræmia should be less than that by a healthy individual is to be expected, because his food nitrogen is less. But he may be excreting quite as large a proportion of urea as would a normal person upon the same diet.

We have found no experiment in which a healthy boy of the same age as our patient took exactly the same amount of food nitrogen as he did. Therefore we cannot say whether a healthy boy and a boy with subacute Bright's disease, each having the same quantity of food nitrogen, would excrete equal amounts of urea or not. But we can determine the percentage of the total nitrogen in the urine which is in the form of urea, and thus find out whether the proportion of urea is diminished in Bright's disease and uræmia or not.

In the following table are summarised the results obtained by different observers in healthy persons. Few complete investigations by the Mörner-Sjöquist process have yet been carried out; we have therefore included some less recent figures, obtained by modified hypobromite methods. In one case only was the diet solely milk. In all cases the total nitrogen was determined by Kjeldahl.

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TABLE III.—*The Urea Nitrogen Relations found by different Observers in the Urine of Healthy Persons.*

Observer.	Date.	Patient's		Diet.	Duration of observation in days.	Method of estimating urea.	The urea nitrogen expressed per cent. of total nitrogen in urine.		
		Sex.	Age.				Minimum.	Maximum.	Average.
Pflüger and Bohland (46) . .	1886	Themselves		Mixed	?	Pflüger-Bohland	84·0	90·3	86·8
Horton-Smith (28) . . .	1887	Himself		Peptonised milk	3	Pflüger-Hüfner	83·8	87·0	85·3
„	1887	Himself		Mixed	3	„	81·2	83·8	82·2
Bohland (6)	1888	Himself		„	?	Pflüger-Bohland	—	—	85·0
Schultze (55)	1889	Himself		Various	?	Schlösing-Bohland	83·8	89·6	86·8
Gumlich (20)	1893	Himself		Mixed	24	Phosphotungstic acid	78·8	88·8	84·0
Camerer (8)	1896	Himself		„	14 observations	Hüfner	83·8	90·5	87·3
„	1896	Himself		Meat	5	„	—	—	93·8
„	1896	Himself		Vegetable	2	„	—	—	86·9
„	1896	Himself		„	2	„	—	—	85·8
„	1896	Himself		Meat	3	„	—	—	88·3
Dunlop (12)	1896	M.	35	Mixed	4	Pflüger-Bohland	81·0	88·9	86·2
„	1896	M.	42	„	3	„	77·5	84·1	80·1
„	1896	M.	40	„	3	„	77·5	84·3	81·2
Camerer (9)	1897	M.	56	„	?	Mörner-Sjöquist	—	—	89·9
„	1897	F.	16	„	?	„	—	—	86·3
„	1897	M.	63	„	?	„	—	—	88·1
„	1897	Himself		„	7 observations	„	87·6	93·7	90·3
Goodbody (19)	1900	M.	?	„	6	„	70·5	89·3	84·0
„	1900	M.	?	„	4	„	84·2	92·0	87·6
Macleod (39)	1901	?	?	Flesh	?	„	—	—	96·1
„	1901	?	?	Creatinin free	?	„	—	—	82·5
Joslin (29)	1901	F.	?	Mixed	15	Squibbs	80·6	94·4	83·9
Hale White and Spriggs (22) .	1901	F.	38	„	55	Mörner-Sjöquist	67·5	96·4	87·3

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Referring to the results obtained by the Mörner-Sjöquist process only, it will be seen that the percentage of the total nitrogen in the urine, which is present as urea nitrogen, may, in health, be as low as 67·5 per cent., or as high as 96·4 per cent. These are extreme variations. Hale White and Spriggs, in a series of twenty-seven consecutive observations upon the same person, found an average of 87·3 per cent.

The averages obtained by the other workers quoted vary from 80·1 per cent. to 93·8 per cent.

In none of the metabolism experiments upon Bright's disease have we found the urea estimated at the same time as the total nitrogen. Prior (50) gives figures for the urea, by Pflüger's method, in some cases; but when reduced to nitrogen the urea nitrogen and the total nitrogen are identical. P. Müller (45), we believe, estimated the urea, but we have been unable to obtain the inaugural dissertation which contains his researches.

Gumlich (20), in occasional samples of urine from patients with chronic parenchymatous nephritis, estimated the urea as nitrogen not precipitated by phosphotungstic acid; and found the proportion of urea nitrogen to vary from 72·3 per cent. to 88·9 per cent. of the total nitrogen in the urine. He made no allowance for the coagulable proteid nitrogen.

Our own results are given in detail in Table I. We have calculated the percentage relation of the urea nitrogen both to the total nitrogen in the urine and to the urinary nitrogen remaining after deduction of that present as coagulable proteid. Below we give the results summarised—

1. For the whole period.
2. For the period of uræmia.
3. For the non-uræmic period.
4. For the different diets.

At first sight the percentage of urea nitrogen appears distinctly lower than in health, the average for the whole period being 75·6 per cent., as against 87·3 per cent. in Hale White and Spriggs' case.

But when we deduct from the total nitrogen of the urine that of the abnormal constituent, coagulable proteid, the urea nitrogen forms 83·4 per cent. of the remainder, the extreme daily variations being 71·8 per cent. and 94·6 per cent. Regarding the coagulable proteid, in this way, as an accidental impurity,

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Table IV.

		Per cent. of urea nitrogen referred to total urinary nitrogen.		Per cent. of urea nitrogen referred to total urinary nitrogen *minus* coagulable proteid nitrogen.		Urea as such, total in grammes.		Grammes of urea as such in 100 c.c. urine.	
		Date.		Date.		Date.		Date.	
Whole period.—February 19th to March 31st	Maximum	Feb. 24	86·056	Feb. 24	94·608	Mar. 27	18·00	Mar. 5	3·13
	Minimum	Mar. 11	67·349	Mar. 21	71·825	Mar. 4	5·76	Mar. 28	0·55
	Average	—	75·13	—	83·36	—	11·54	—	1·27
Period of mild uræmia.—March 2nd to 13th	Maximum	Mar. 5	77·141	Mar. 5	85·467	Mar. 2	12·36	Mar. 5	3·13
	Minimum	Mar. 11	67·349	Mar. 11	75·118	Mar. 4	5·76	Mar. 13	1·23
	Average	—	72·48	—	82·03	—	8·32	—	2·07
Whole period *minus* uræmic period. — February 19th to March 1st, and 14th to 31st	Maximum	Feb. 24	86·056	Feb. 24	94·608	Mar. 27	18·00	Feb. 25	2·36
	Minimum	Feb. 20	68·846	Mar. 21	71·825	Mar. 16	8·18	Mar. 28	0·55
	Average	—	77·11	—	84·42	—	12·58	—	1·01
Milk diet only.—February 19th to March 4th, and 18th to 22nd	Maximum	Feb. 24	86·056	Feb. 24	94·608	Feb. 21	14·02	Mar. 4	2·77
	Minimum	Feb. 20	68·846	Mar. 21	71·825	Mar. 4	5·76	Mar. 18	0·90
	Average	—	75·13	—	83·36	—	11·54	—	1·27
Diet of biscuits or bread and milk.—March 5th to 17th	Maximum	Mar. 14	79·630	Mar. 15	87·280	Mar. 17	11·72	Mar. 5	3·13
	Minimum	Mar. 11	67·349	Mar. 11	75·118	Mar. 12	6·26	Mar. 16	1·09
	Average	—	74·08	—	82·98	—	8·57	—	1·67
Diet of milk, biscuits, and Liebig. —March 23rd to 31st	Maximum	Mar. 29	83·957	Mar. 27	87·642	Mar. 27	18·00	Mar. 23	1·18
	Minimum	Mar. 28	69·115	Mar. 28	73·850	Mar. 31	10·39	Mar. 28	0·55
	Average	—	78·16	—	84·196	—	14·88	—	0·79

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the proportion of urea nitrogen in our case was therefore within the limits found in health.

As regards the uræmic period, the urea nitrogen formed, on an average, 82·03 per cent. of the urinary nitrogen after deduction of that in the coagulable proteid. This is slightly less than 84·42 per cent., the average proportion for the remainder of the time. But in Section V it is shown that the proportion of uric acid was at its maximum during the uræmic period; this will partly account for the slightly lower proportion of urea nitrogen. In our patient, therefore, the onset of uræmic symptoms was accompanied by no marked relative decrease in the urea nitrogen.

The urea in 100 c.c. urine, on the other hand, rose considerably at this time. The average for the uræmic period was 2·07 grammes of urea in 100 c.c. urine, whereas for the remainder of the time it was 1·01 grammes. The reason of this was the smaller volume of urine passed, and its consequent greater concentration.

The influence of the different diets is also little marked. It will be seen in Table IV that the urea nitrogen formed a slightly greater percentage of the whole when Liebig was given than without it; but, whether the coagulable proteid nitrogen be reckoned or be previously deducted, the variations caused by diet were slight.

The conclusions, therefore, which we draw from this section of our work are, that in our patient with subacute nephritis—

1. There was no diminution of the proportion of urea nitrogen to the total nitrogen of the urine, if the coagulable proteid be regarded as an accidental body, and its nitrogen first deducted from the total; but that, reckoning the nitrogen of this abnormal body in the total, the proportion of urea nitrogen was about 10 per cent. below the normal.

2. The proportion of urea nitrogen to total urinary nitrogen was not appreciably lower when uræmic symptoms showed themselves than at other times; the total urea nitrogen was less during uræmia, as the food was less, whilst the percentage of urea in the urine rose considerably.

3. The addition of bread, biscuit, or Liebig's extract of meat to a purely milk diet caused no corresponding alteration in the proportion of the urea nitrogen.

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Section V.

The uric acid.

In Osler's 'Principles and Practice of Medicine,' p. 409, there is a quotation from Kolisch (30) to the effect that in nephritis the uric acid is diminished and the xanthin bases in the urine increased. In his original paper Kolisch states that in nephritis the total alloxuric bodies remain constant, but that there is an increase in the xanthin bases (xanthin, hypoxanthin, paraxanthin, adenin, guanin, carnin) at the expense of the uric acid. He quotes Baginsky (3), who found that in children with nephritis the xanthin in the urine increases.

Kolisch and Dostal (30) estimated the total alloxuric bodies by the method of Krüger and Wulff (34), the uric acid by the Ludwig- (38) Salkowski (53A) process. In health they give the proportion—

$$\frac{\text{Uric acid nitrogen}}{\text{Xanthin base nitrogen}} = \frac{4}{1};$$

and this is confirmed by Kossel's pupils, quoted by Zuelzer (69), whilst Weintraud (67) found $\frac{5}{1}$ and $\frac{7}{1}$. In nephritis their analyses showed for single day estimations with different patients:

$$\frac{\text{Uric acid nitrogen}}{\text{Xanthin base nitrogen}} = \frac{\cdot 24}{1}, \quad \frac{\cdot 24}{1}, \quad \text{and} \quad \frac{\cdot 59}{1}.$$

The nitrogen of the total alloxuric bodies in these cases was 0·152 gramme, 0·220 gramme, and 0·312 gramme respectively, whilst in health they found 0·260 gramme. They draw the conclusion that one of the functions of the kidney is to convert the xanthin bases into uric acid, and that in nephritis this change does not take place.

Frerichs (15), Bartels (5), Dickinson (10), Fleischer (14), Wagner (66), and Rosenstein (51), using Heintz's (23) method, found the uric acid diminished in Bright's disease. Géza Fodor (17), by the Ludwig-Salkowski (53A) process, obtained similar results to those of Kolisch and Dostal as regards xanthin bases and uric acid, and further found that the fall of uric acid in the urine of nephritis was unaccompanied by any rise of uric acid in the blood.

On the other hand, many investigators have been unable to

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TABLE V.

Observer.	Date.	Total daily uric acid in grammes.	Form of nephritis.	Uric acid relations.		Methods.		
				Uric acid nitrogen to total urinary nitrogen.	Uric acid as such to urea as such.	For total nitrogen.	For urea.	For uric acid.
Stadthagen (59) .	1887	0·3 to 0·5	Nephritis	—	$\frac{1}{80}$ to $\frac{1}{60}$	—	?	Salkowski
Prior (50) . .	1891	0·6 to 0·7	Acute nephritis	$\frac{1}{68}$ to $\frac{1}{57}$	—	Kjeldahl	—	Fokker-Salkowski
„ . .	1891	0·3 to 0·5	Chronic interstitial	$\frac{1}{103}$ to $\frac{1}{90}$	—	„	—	„
„ . .	1891	0·3 to 0·9	Sclerosis of kidney	$\frac{1}{68}$ to $\frac{1}{39}$	—	„	—	„
„ . .	1891	0·2 to 0·5	Chronic parenchymatous	$\frac{1}{137}$ to $\frac{1}{78}$	—	„	—	„
Van Ackeren (63) .	1892	0·3 to 1·0	Acute nephritis	—	$\frac{1}{52}$ to $\frac{1}{17}$	—	Pflüger-Liebig	Ludwig-Salkowski
„ .	1892	0·3 to 0·7	„	—	$\frac{1}{30}$ to $\frac{1}{16}$	—	„	„
„ .	1892	0·7 to 1·0	„	—	$\frac{1}{40}$ to $\frac{1}{21}$	—	„	„
„ .	1892	0·3 to 1·2	„	—	$\frac{1}{46}$ to $\frac{1}{26}$	—	„	„
„ .	1892	0·2 to 0·5	Chronic parenchymatous	—	$\frac{1}{41}$ to $\frac{1}{26}$	—	„	„
„ .	1892	0·6 to 0·9	„ „	—	$\frac{1}{36}$ to $\frac{1}{34}$	—	„	„
„ .	1892	0·4 to 0·6	„ „	—	$\frac{1}{52}$ to $\frac{1}{25}$	—	„	„
„ .	1892	0·7 to 1·5	Granular kidney	—	$\frac{1}{16}$ to $\frac{1}{7}$	—	„	„
„ .	1892	0·6 to 0·8	„	—	$\frac{1}{37}$ to $\frac{1}{23}$	—	„	„
„ .	1892	0·2 to 0·5	„	—	$\frac{1}{81}$ to $\frac{1}{23}$	—	„	„
Zuelzer (69) . .	1896	0·5	?	$\frac{1}{51}$	—	Kjeldahl	—	„
„ . .	1896	0·5	?	$\frac{1}{48}$	—	„	—	„
„ . .	1896	0·7	?	$\frac{1}{50}$	—	„	—	„
„ . .	1896	0·4	?	$\frac{1}{63}$	—	„	—	„
Milroy and Malcolm (43) . .	1898	0·1 to 0·6	Granular kidney	$\frac{1}{56}$	—	„	—	„
Haig (21) . .	1900	3·7 grains	Nephritis (in a child of 5)	—	$\frac{1}{35}$	—	Hüfner	Haycraft-Salkowski

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TABLE VI.—*Uric acid relations in healthy people.*

Observer.	Date.	Total daily uric acid in grammes.	Diet.	Uric acid relations.		Methods.		
				Uric acid nitrogen to total nitrogen in urine.	Uric acid as such to urea as such.	For total nitrogen.	For urea.	For uric acid.
Horton-Smith (28)	1888	·3 to ·4	Milk	—	$\frac{1}{80}$	—	Pflüger-Hüfner	Salkowski
„	1888	·3 to ·4	Peptonised milk	$\frac{1}{133}$	$\frac{1}{94}$	Kjeldahl	„	„
„	1888	·6 to ·8	Mixed	$\frac{1}{79}$	$\frac{1}{47}$	„	„	„
Yvon and Berlioz (68)	1888	—	„	—	$\frac{1}{80}$	—	?	?
„ „	1888	—	„	—	$\frac{1}{40}$	—	?	?
Schultze (55)	1889	·7 to 1·5	„	—	$\frac{1}{65}$ to $\frac{1}{29}$	—	Schlösing-Bohland	Fokker
Pott (47)	1889	·5 to 1·2	„	$\frac{1}{80}$ to $\frac{1}{30}$	—	Kjeldahl	—	Fokker-Salkowski
Schöndorff (54)	1890	·7 to 1·3	„	$\frac{1}{75}$ to $\frac{1}{20}$	—	„	—	„
Herringham and Groves (24)	1891	—	„	—	$\frac{1}{30}$	—	Hypobromite corrected	Ludwig-Salkowski
Umber (62)	1896	·5 to 1·6	„	$\frac{1}{71}$ to $\frac{1}{38}$	—	Kjeldahl	—	„
„	1896	·7 to 1·0	„	$\frac{1}{53}$ to $\frac{1}{41}$	—	„	—	„
„	1896	·4 to ·9	„	$\frac{1}{90}$ to $\frac{1}{78}$	—	„	—	„
Strauss (60)	1896	·4 to ·7	„	$\frac{1}{63}$ to $\frac{1}{47}$	—	„	—	Salkowski
„	1896	·9 to 1·4	Mixed and Liebig	$\frac{1}{54}$ to $\frac{1}{32}$	—	„	—	„
Hopkins and Hope (27)	1898	·5 to ·8	Various	—	$\frac{1}{44}$ to $\frac{1}{31}$	—	Knop-Hüfner and Mörner-Sjöquist	Hopkins
Smith-Jerome (57)	1898	·4 to ·8	Mixed	$\frac{1}{139}$ to $\frac{1}{78}$	—	Kjeldahl	—	Ludwig-Salkowski
Bain and Edgecombe (4)	1898	·7	„	—	$\frac{1}{54}$	—	Hypobromite	Hopkins
„ „	1898	·5	„	—	$\frac{1}{64}$	—	„	„
Milroy and Malcolm (43)	1898	·8	„	$\frac{1}{80}$	—	Kjeldahl	—	Ludwig-Salkowski
Goodbody (19)	1900	·6 to ·8	„	$\frac{1}{102}$ to $\frac{1}{79}$	$\frac{1}{69}$ to $\frac{1}{40}$	„	Mörner-Sjöquist	Hopkins & Salkowski
„	1900	·7 to ·8	„	$\frac{1}{70}$ to $\frac{1}{69}$	$\frac{1}{48}$ to $\frac{1}{39}$	„	„	„ „
Haig (21)	1900	—	?	—	$\frac{1}{35}$ to $\frac{1}{33}$	—	Hüfner	Haycraft-Salkowski
Smith-Jerome (58)	1900	·5	Mixed	$\frac{1}{67}$	—	Kjeldahl	—	Ludwig-Salkowski
„	1900	·6	Mixed and Liebig	$\frac{1}{65}$	—	„	—	„
Tunnicliffe and Rosenheim (61A)	1900	·05 to ·25	Milk chiefly	$\frac{1}{210}$ to $\frac{1}{67}$	—	„	—	Salkowski
„ „	1900	·04 to ·22	„	$\frac{1}{230}$ to $\frac{1}{130}$	—	„	—	„
„ „	1900	·18 to ·23	„	$\frac{1}{85}$ to $\frac{1}{67}$	—	„	—	„
„ „	1900	·05 to ·19	„	$\frac{1}{180}$ to $\frac{1}{143}$	—	„	—	„

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demonstrate any such fall. Vogel (65), though he used Heintz's method, found as much uric acid in acute nephritis as in health; and the following more recent workers, employing the Ludwig-Salkowski or Hopkins (26) processes, confirm this (*see* Table V).

Zuelzer (69) further states that he never found the uric acid in Bright's disease less than the xanthin bases, his ratio—

$$\frac{\text{Uric acid nitrogen}}{\text{Xanthin base nitrogen}}$$ varying from $\frac{1{\cdot}3}{1}$ to $\frac{35}{1}$ to $\frac{\infty}{|}$;

whilst Umber's (62) figures for healthy persons show variations between $\frac{3{\cdot}7}{1}$ and $\frac{36{\cdot}6}{1}$.

The following table shows the values for uric acid in health, obtained by modern methods (*see* Table VI).

It will be seen that there are very wide variations in the uric acid, even in health. The ratio $\frac{\text{uric acid}}{\text{urea}}$ in Table VI varies from $\frac{1}{94}$ to $\frac{1}{30}$; and the ratio $\frac{\text{uric acid nitrogen}}{\text{total urinary nitrogen}}$ from $\frac{1}{240}$ to $\frac{1}{38}$. In Table V, of Bright's disease, the ratio $\frac{\text{uric acid}}{\text{urea}}$ ranges from $\frac{1}{84}$ to $\frac{1}{7}$, and $\frac{\text{uric acid nitrogen}}{\text{total urinary nitrogen}}$ from $\frac{1}{137}$ to $\frac{1}{39}$. Therefore Kolisch's statement, quoted by Osler, is not supported by the results of more recent analyses.

Our own results are given in full in Table I. The most remarkable point, perhaps, is the almost constant and relatively high ratio $\frac{\text{uric acid}}{\text{urea}}$ during the period of mild uræmia, March 2nd to 13th inclusive. This ratio is quite as high, but slightly less constant, during the last nine days of the experiment, when Liebig's meat extract was added to the diet. During the remaining twenty days the ratio was very variable, and the mean much lower, as shown in the following summary:

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TABLE VII.

	Ratio of uric acid nitrogen to total nitrogen of urine.			Ratio of uric acid as such to urea as such.			Total daily uric acid in grms.		
	Max.	Min.	Aver.	Max.	Min.	Aver.	Max.	Min.	Aver.
For the whole experiment (41 days)	$\frac{1}{25}$	$\frac{1}{250}$	$\frac{1}{38}$	$\frac{1}{31}$	$\frac{1}{114}$	$\frac{1}{48}$	0·48	0·12	0·24
For the uræmic period (12 days)	$\frac{1}{26}$	$\frac{1}{50}$	$\frac{1}{38}$	$\frac{1}{38}$	$\frac{1}{45}$	$\frac{1}{38}$	0·29	0·15	0·22
For the remaining period without Liebig (20 days)	$\frac{1}{21}$	$\frac{1}{250}$	$\frac{1}{111}$	$\frac{1}{33}$	$\frac{1}{134}$	$\frac{1}{63}$	0·27	0·12	0·18
For the remaining period with Liebig (9 days)	$\frac{1}{25}$	$\frac{1}{31}$	$\frac{1}{26}$	$\frac{1}{31}$	$\frac{1}{46}$	$\frac{1}{38}$	0·48	0·31	0·39

The ratio $\frac{\text{uric acid nitrogen}}{\text{total urinary nitrogen}}$ is more variable and of less value than that of $\frac{\text{uric acid}}{\text{urea}}$, on account of the varying quantities of coagulable proteid in the urine.

The high ratio $\frac{\text{uric acid nitrogen}}{\text{total urinary nitrogen}}$ when Liebig was given corresponds to the results obtained by Strauss (60) and Smith-Jerome (57) with meat extract feeding in the healthy subject.

We conclude that, in our patient suffering from subacute nephritis—

1. The uric acid was not diminished out of proportion to the other urinary constituents.

2. The variations in the ratio $\frac{\text{uric acid}}{\text{urea}}$ are not greater than those which occur in health.

3. The ratio $\frac{\text{uric acid}}{\text{urea}}$ became higher and much more constant with advent of uræmic symptoms.

4. The addition of extract of meat to the diet produced, as in health, both an actual and a relative increase in the uric acid.

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Section VI.

The coagulable proteid.

Albumen is present in the urine of Bright's disease in such variable quantities that we have not much to say about it in the present instance. Great care was taken in the estimation of the coagulable proteid nitrogen, but the deductions we can draw are few.

The results have enabled us, however, in Section IV, to deduct albumen nitrogen from total nitrogen, and to find the relation of the urea nitrogen to the remainder, and we concluded that the coagulable proteid might be regarded as a foreign or adventitious substance.

We made no attempt to differentiate the varieties of coagulable proteid present.

Van Noorden and Ritter (64), estimating the albumen by Scherer's method, conclude, from figures tabulated on p. 223 of their paper, that the *kind* of diet has little effect upon the amount of albumen in the urine; but that when there is a *change* of diet there is often an increase in the albumen for a few days after the change. The following table is a summary of our results:

Table VIII.

	Nitrogen as coagulable proteid in 24 hours in grms.	Per cent. of nitrogen as coagulable proteid referred to total nitrogen in urine.
Average of whole period (41 days) .	0·6536	9·348 per cent.
Average of 11 days in uræmic period. (There was no estimation on March 6th)	0·6085	11·640 „
Influence of *kind* of diet:		
Average of 18 days milk only . .	0·7080	9·884 „
Average of 12 days milk and bread or biscuits	0·5700	10·680 „
Average of 9 days milk, biscuit, and Liebig	0·6375	7·184 „
Influence of *change* of diet:		
Average of last 2 days of milk, before bread	0·5500	—
Average of first 2 days of bread .	0·4479	—
Average of last 2 days of milk, before Liebig	0·5417	—
Average of first 2 days of Liebig .	0·6948	—

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If any conclusions can be drawn at all, we should infer from Table VIII that the average daily output of coagulable proteid in the urine was almost constant in the different periods; that the addition of bread or Liebig to our patient's diet did not cause it to alter much; that in the uræmic period the average total for each twenty-four hours was approximately the same as the average for the whole period; and that the average daily total was more constant than the average percentage relationship to the total nitrogen in the urine.

It is true that when Liebig was added to the diet there was an increase in the coagulable proteid for the first few days; the last two days with milk diet, before Liebig was given, gave an average of 0·5417 gramme nitrogen as albumen; the average of the first two days of Liebig was 0·6948 gramme nitrogen. The average for the whole Liebig period (0·6375 gramme), on the other hand, was less than the average for the whole period of milk diet (0·708 gramme). The change, however, from milk to milk and bread or biscuit gave a fall in coagulable proteid nitrogen from 0·55 gramme to 0·4479 gramme. We do not find, therefore, as Van Noorden (64) did, that *change* of diet always caused an increase in the albumen.

The detailed figures in Table I show the coagulable proteid nitrogen to have been highest on March 1st and 2nd, namely, on the first day of distinct uræmia and on the day before it, but this may be mere coincidence. It is of interest to compare the figures with the clinical account; it will be seen that the œdema was, as far as we could judge, most marked about March 20th; the coagulable proteid nitrogen was by no means at its maximum at this time. The total amount of coagulable proteid in the urine gave no close index of the œdema present.

Section VII.

The nitrogen as "other bodies."

No attempt was made to determine what the "other bodies" were. They were calculated by subtracting the urea nitrogen, the uric acid nitrogen, and the coagulable proteid nitrogen on the one hand, from the total nitrogen in the urine on the other.

The following table gives the average percentage relation of

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"other bodies" nitrogen to total urinary nitrogen for the different periods:

TABLE IX.

	Per cent. of "other bodies" nitrogen referred to total urinary nitrogen as 100.
Whole period— February 19th to March 31st	13·88 per cent.
Uræmic period— March 2nd to March 13th	14·52 „
Non-uræmic period— February 19th to March 1st, and March 14th to March 31st	13·60 „
Milk diet only— February 19th to March 4th, and March 18th to March 22nd	14·08 „
Milk and bread or biscuit— March 5th to March 17th	13·92 „
Milk and biscuit and Liebig— March 23rd to March 31st	13·24 „

We draw no conclusions from Table IX. The figures are averages; the daily variations, which were considerable, are given in Table II. It is of interest to note how the average proportion of "other bodies" nitrogen remains almost constant throughout, in spite of alterations in the patient's general condition and in his diet.

SECTION VIII.

The fæces.

Part of the treatment of Bright's disease is usually directed towards increasing the intestinal elimination, with a view to diminishing the work of the kidneys. Unfortunately it is not yet possible to determine how much of the nitrogen in the fæces is derived from food unabsorbed, and how much, if any, from metabolic end products excreted into the bowel. Nevertheless it is interesting to compare the nitrogen in the fæces of persons

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TABLE X.

Name of observer.	Date.	Patient's			Duration of experiment in days.	Diet.	Nitrogen in fæces.		Average nitrogen in fæces per diem in grms.
		Sex.	Age.	Weight in kgs.			Per cent. referred to nitrogen intake.	Per cent. referred to total nitrogen in urine and fæces.	
Rubner (52)	1879	M.	27	—	3	Milk only	6·5	6·9	1·0
Hofman (25)	1880	M.	—	66	2 × 3*	„	11·1	7·7	1·4
Slatkowski (56)	1880	M.	—	—	3 × 3*	„	5·8	6·4	1·6
„	1880	M.	—	—	3 × 3*	„	4·2	4·2	0·8
„	1880	F.	—	—	3	„	4·9	7·5	1·0
Laptschinsky (35)	1880	M.	26	55	6	Milk and a little bread	4·0	6·4	0·8
„	1880	M.	46	62	7	„ „	7·6	6·2	1·3
„	1880	M.	22	65	6	„ „	5·1	5·1	1·0
„	1880	M.	23	67	6	„ „	11·1	11·6	2·2
„	1880	M.	24	73	5	„ „	6·1	5·4	0·8
Camerer (7)	1882	F.	12	—	3	Milk only	4·9	4·9	0·5
„	1882	F.	10	—	3	„	3·7	4·0	0·4
„	1882	M.	$6\frac{3}{12}$	—	3	„	5·4	4·4	0·5
„	1882	F.	$5\frac{10}{12}$	—	3	„	7·4	6·5	0·6
„	1882	F.	$4\frac{3}{12}$	—	3	„	9·2	8·8	0·8
Rudenko (53)	1885	M.	—	70	3	„	5·5	4·5	0·8
„	1885	M.	—	105	5	„	6·7	4·8	0·8
„	1885	M.	44	51	15	„	3·6	3·1	0·4
„	1885	F.	35	44	16	„	24·7	22·0	2·2
„	1885	M.	62	61	8	„	14·7	15·3	2·1

* This means that there were two experimental periods of three days.

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TABLE X—*continued.*

Name of observer.	Date.	Patient's			Duration of experiment in days.	Diet.	Nitrogen in fæces.		Average nitrogen in fæces per diem in grms.
		Sex.	Age.	Weight in kgs.			Per cent. referred to nitrogen intake.	Per cent. referred to total nitrogen in urine and fæces.	
Markov (42)	1888	M.	28	—	8	Milk only	5·1	5·6	1·2
„	1888	M.	29	—	8	„	6·6	6·8	1·5
„	1888	M.	26	—	2 × 8*	„	4·3	4·7	1·0
„	1888	M.	24	—	6	„	6·1	5·4	1·0
„	1888	M.	24	—	8	„	5·9	6·5	1·3
Prausnitz (48)	1889	M.	—	74	3	„	8·3	5·5	1·1
Listov (37)	1892	F.	21	59	2 × 3*	Milk and bread	6·2	7·0	1·4
„	1892	F.	24	50	2 × 3*	„ „	6·3	7·4	1·3
„	1892	F.	22	64	4 × 3*	„ „	7·1	7·3	1·6
„	1892	F.	19	52	2 × 3*	„ „	6·1	7·4	1·3
„	1892	F.	19	48	2 × 3*	„ „	6·9	8·1	1·3
„	1892	F.	19	77	2 × 3*	„ „	7·2	7·4	1·7
„	1892	F.	19	67	2 × 3*	„ „	9·8	10·2	2·3
Magnus Levy (40)	1893	M.	16	57	3	Milk only	4·9	4·1	0·8
„	1893	Same boy		—	3	Milk, bread, butter, sugar	8·6	8·7	1·5
Tunnicliffe and Rosenheim (61A)	1901	M.	2½	15	25	Milk chiefly	9·9	11·2	0·6
„ „	1901	M.	5	19	22	„	11·0	11·9	0·9
„ „	1901	M.	2½	15	7	„	8·6	10·1	0·6
„ „	1901	M.	5	17	7	„	8·1	9·7	0·6

* This means that there were two experimental periods of three days.

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suffering from Bright's disease with that in the fæces of healthy people.

Some observers compare the fæces nitrogen with the total nitrogen intake, regarding the former as loss, the difference between the two as the true intake, and the relation between the two as an index of the assimilative power.

This can only be true if no nitrogenous bodies are excreted by the bowel. Pregl (49) has shown that excretory products, such as urea and ammonia, may be found in the intestinal secretion; it seems, therefore, justifiable to compare the fæces nitrogen with the total output of nitrogen in the urine and fæces together, as well as with the nitrogen in the food intake. An additional argument for so doing arises from the fact that in many cases the food nitrogen has been calculated from diet tables, and therefore may be less accurate than the figures obtained by direct Kjeldahl estimations of the urine and fæces. In the following tables both relations are given.

In the first are the results obtained by different observers in normal people. A very large number of fæces determinations has been found in the literature, but for purposes of comparison with our own, only those in which the diet has been chiefly milk have been tabulated, and no case given in which the observation extended over less than three days.

In one case of Rudenko's as much as 24·7 per cent. of the nitrogen of the intake was found in the fæces, but in no other case are the figures so high. Including this exceptional instance, the average results of thirty-seven investigations upon different healthy persons having a milk diet showed that for every 100 grammes of nitrogen in the food there were 7·4 grammes of nitrogen in the fæces; and for every 100 grammes of nitrogen in the urine and fæces there were 7·3 grammes of nitrogen in the fæces, and the average daily total nitrogen in the fæces was 1·2 grammes.

Camerer's experiments alone were made upon boys and girls of an age similar to that of our patient, and the figures, an average of five cases, are as follows:—For every 100 grammes nitrogen in the food there were 6·1 grammes in the fæces; for every 100 grammes nitrogen in the urine and fæces there were 5·7 grammes nitrogen in the fæces, the daily average total nitrogen in the fæces being 0·6 gramme.

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TABLE XI.

Name of observer.	Date.	Patient's			Duration of experiment in days.	Diet.	Nitrogen in fæces.		Form of nephritis.	Average nitrogen in fæces per diem in grms.
		Sex.	Age.	Weight in kgs.			Per cent. referred to nitrogen intake.	Per cent. referred to nitrogen in urine and fæces.		
Rudenko (53) . .	1885	M.	30	68	18	?	20·0	11·9	Diffuse nephritis	1·5
,, . .	1885	M.	51	58	20	?	10·2	12·2	,, ,,	0·9
,, . .	1885	F.	28	75	7	?	20·0	13·4	,, ,,	1·5
Korkounov (31) .	1886	M.	—	69	2 × 4 4 × 3	Milk	8·2	9·9	Chronic nephritis	2·0
,, .	1886	M.	—	76	3 and 5	,,	74·2	46·4	,, ,,	11·6
Evdokimov (13) .	1887	M.	26	57	13*	Milk, bread, tea	21·0	22·1	Acute parenchymatous	2·5
Garine (16) . .	1887	M.	48	53	15*	Mixed	10·7	13·8	Acute interstitial	3·1
,, . .	1887	M.	39	75	15*	,,	31·1	39·0	,, ,,	6·2
Grigoriev (18) . .	1888	M.	22	64	13*	Various, but chiefly milk and bread	5·0	4·2	Acute parenchymatous	0·6
,, . .	1888	M.	51	81	9*		3·0	2·7	Chronic parenchymatous	0·3
,, . .	1888	M.	27	79	40*		43·9	32·3	,, ,,	5·0
,, . .	1888	M.	25	62	25*		17·1	13·9	,, ,,	2·3
Prior (50). . .	1891	M.	19	—	15*	Various	4·6	4·7	Nephritis	0·7
,, . . .	1891	M.	40	—	21*	,,	5·1	5·2	Bright's disease	0·7
,, . . .	1891	M.	57	—	16*	,,	7·4	10·0	Sclerosis of kidney	0·8
,, . . .	1891	M.	34	—	9*	,,	5·3	6·4	Chronic parenchymatous	0·9

* In these cases the experiment was not continuous, and various diets and drugs were given.

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TABLE XI—*continued.*

Name of observer.	Date.	Patient's			Duration of experiment in days.	Diet.	Nitrogen in fæces.		Form of nephritis.	Average nitrogen in fæces per diem in grms.
		Sex.	Age.	Weight in kgs.			Per cent. referred to nitrogen intake.	Per cent. referred to nitrogen in urine and fæces.		
Prior (50) . .	1891	M.	47	—	10*	Various	13·4	12·0	Chronic parenchymatous	1·3
„ . .	1891	M.	47	—	19*	„	9·3	9·7	Chronic interstitial	1·0
P. Müller (45) . .	1891	F.	25	—	33*	Mixed	10·9	12·9	Chronic nephritis	1·5
Van Noorden (64) .	1891	F.	37	—	5	„	16·4	22·7	Shrivelled kidney	2·9
„ .	1891	F.	27	46	7	„	14·6	14·1	„ „	1·8
„ .	1891	F.	38	56	9	„	4·5	5·6	„ „	0·6
„ .	1891	F.	43	50	16*	„	5·2	5·6	„ „	0·7
„ .	1891	F.	22	78	27	„	11·3	11·1	Chronic parenchymatous	1·6
Mann (41) . .	1892	M.	45	—	12*	Various	19·5	26·8	„ „	2·1
„ . .	1892	M.	53	—	6*	„	11·4	17·0	Sclerosis of kidneys	2·0
„ . .	1892	M.	29	—	5*	„	8·6	10·3	„ „	1·5
Kornblum (32) .	1892	M.	49	62	15*	Mixed	3·1	3·6	Chronic nephritis	0·4
Baginsky (3A) . .	1893	F.	13½	22	5	Milk	5·6	6·4	Acute nephritis	0·7
„ . .	1893	F.	13¾	28	5	„	4·3	4·8	Scarlatinal nephritis	0·6
„ . .	1893	F.	5	14	6	„	10·0	14·6	Acute nephritis	1·3
„ . .	1893	F.	12	27	3	Milk, rice, bread	17·7	21·7	„ „	2·1

* In these cases the experiment was not continuous, and various diets and drugs were given.

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In the next table the figures obtained upon persons suffering from different forms of Bright's disease are tabulated. In these the diet was not always milk only, though it was always light, and in some of them drugs were given (*see* Table XI).

It will be seen that Korkounov on one occasion found as much as 74·2 per cent. of the nitrogen intake in the fæces, and Grigoriev 43·9 per cent.; but these figures are very much above the average. The lowest figures are also Grigoriev's, namely, 3 per cent. of the nitrogen intake, and 2·7 per cent. of the total nitrogen in the urine and fæces.

The average of the whole thirty-two cases shows that for every 100 grammes of nitrogen in the food there were 14·1 grammes nitrogen in the fæces; for every 100 grammes of nitrogen in the urine and fæces there were 14·0 grammes nitrogen in the fæces, the average daily nitrogen in the fæces being 1·9 grammes.

Baginsky's patients alone approach in age to ours, and the average of his results for four observations are as follows:—For every 100 grammes of nitrogen in the food there were 9·4 grammes nitrogen in the fæces; for every 100 grammes of nitrogen in the urine and fæces there were 12·0 grammes nitrogen in the fæces, the average daily nitrogen in the fæces being 1·2 grammes.

The table shows that very wide variations in the fæces nitrogen in Bright's disease may occur quite independently of the form of kidney lesion.

Our own figures for each day are given *in extenso* in Table I. On some of the days the patient vomited, and the nitrogen of the vomit has been added to the fæces nitrogen. The vomits were always very small, being chiefly saliva. On three days they were estimated by Kjeldahl and found to contain 0·0482 gramme, 0·0407 gramme, and 0·0629 gramme nitrogen respectively. Being so small the vomit was therefore on other occasions added to the daily fæces, and the two estimated together.

The following is a summary of our results arranged as follows:

1. For successive periods of five days each, the first day being neglected.

2. For the period of mild uræmia.

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3. For the different diets the patient took.
4. The average for the entire experiment.

TABLE XII.

	Percentage of nitrogen in fæces referred to nitrogen in food.	Percentage of nitrogen in fæces referred to nitrogen in urine and fæces.	Average nitrogen in fæces per diem in grms.
1. Successive periods of 5 days—			
(*a*) February 20th to February 24th	13·6	14·3	1·3
(*b*) „ 25th to March 1st	18·0	19·7	1·7
(*c*) March 2nd to March 6th	14·0	12·4	0·8
(*d*) „ 7th to „ 11th	20·1	20·6	1·3
(*e*) „ 12th to „ 16th	11·6	13·9	0·8
(*f*) „ 17th to „ 21st	14·0	14·7	1·3
(*g*) „ 22nd to „ 26th	11·3	13·2	1·3
(*h*) „ 27th to „ 31st	11·3	11·4	1·2
2. Period of mild uræmia— March 2nd to March 13th (12 days)	15·9	15·7	1·0
3. Different diets—			
(*a*) Milk—February 19th to March 4th, March 18th to March 22nd	14·9	15·5	1·3
(*b*) Milk and bread or biscuit—March 5th to March 17th	14·9	16·1	1·0
(*c*) Milk and biscuit and Liebig—March 23rd to March 31st	10·9	11·8	1·2
4. Average for entire experiment (41 days)	13·9	14·7	1·2

Van Noorden and Ritter (64) concluded from their researches that the fæces nitrogen might, in Bright's disease, either be almost normal or considerably higher, but that neither from the general condition of the patient nor from the variety of the kidney lesion could it be decided beforehand whether high or normal figures would be found, and that it could not be determined whether the fæces nitrogen was due to non-absorption or to true secretion.

Our own conclusions are that, in our patient, suffering from subacute parenchymatous nephritis, and treated with purgatives:—

1. The average daily fæces nitrogen (1·2 grammes) is the same as that found as the mean of thirty-seven investigations upon healthy persons of all ages upon a milk diet.

2. The average daily fæces nitrogen (1·2 grammes) is double that found as the mean of five investigations by Camerer upon

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healthy children of about the same age as our patient (0·6 gramme).

3. The average daily fæces nitrogen (1·2 grammes) is less than that found as the mean of thirty-two investigations upon patients of all ages suffering from different kinds of Bright's disease (1·9 grammes).

4. The average daily fæces nitrogen (1·2 grammes) is the same as the mean of four investigations by Baginsky upon children suffering from acute nephritis, at ages comparable to that of our patient.

5. The fæces nitrogen for the whole period, expressed as percentage of nitrogen in urine and fæces (14·7 per cent.), is slightly greater than that of four children with acute nephritis investigated by Baginsky (12 per cent.), is more than twice as much as that of thirty-seven different healthy persons upon milk diet (7 per cent.), and nearly three times that of five healthy children upon a milk diet investigated by Camerer (5·7 per cent.).

6. The influence of diet is little marked; with Liebig the proportion of fæces nitrogen (11·8 per cent.) was somewhat less than with milk alone (15·5 per cent.), or with milk and bread (16·1 per cent.).

7. That during the uræmic period the proportion of the fæces nitrogen (15·7 per cent.) did not appreciably differ from that of the whole experiment (14·7 per cent.).

8. The proportion of fæces nitrogen was uniformly high, and did not at any time show wide variations from the average.

Such high proportion, however, does not prove that the bowel was excreting nitrogen, and thus doing work that would otherwise be done by the kidneys, since we have no conclusive evidence that the whole of the fæces nitrogen may not have been due to non-assimilation from the food. In our patient there were three possible sources of fæces nitrogen, namely:

(*a*) Non-assimilation of food.

(*b*) True bowel excretion.

(*c*) Inflammatory exudation from mucous membrane.

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Section IX.

The unrecovered nitrogen.

Our patient's weight was approximately the same at the end of the experiment as at the beginning; therefore the loss of nitrogen (20·7 grammes) in the six weeks may be due either to experimental error or to the sweat and shedding of hair, surface skin, and psoriasis scales. How much is due to the second factor we do not know; in spite of every care, the sum of the experimental errors of forty-one days cannot but be considerable, because milk spilled makes the intake too high, urine spilled the output too low.

Other workers have found wide differences. Referring only to those metabolism experiments in which the diet was milk and the person healthy, we find that Hofman (25) in a three days' observation recovered 30·3 grammes more nitrogen than was in the food; Lapschinsky (35), at the opposite extreme, found in six days a deficit of 45 grammes. Most of the experiments are for short periods only, and the variations are so great that no useful purpose would be served by giving all the results here. They have been summarised in tabular form by Atwater and Langworthy (2).

Tunnicliffe and Rosenheim's experiments upon two healthy children, whose diet was chiefly milk, are of longer duration, and comparable with our own as regards the diet and the patients' ages.

The daily nitrogen deficit is tabulated in their paper (61A).

In Case A, a child aged 2½ years, the deficit was 18·87 grammes in twenty-five days, with an increase of 0·17 kilo. in body-weight. In Case B, a child aged 5 years, it was 14·05 grammes in twenty-two days, the increase in weight being 0·28 kilo.[1]

Turning now to metabolism experiments in Bright's disease, we find even wider variations. Thus Korkounov (31) recovered

[1] In a paper published since this was written ('Journal of Hygiene,' vol. i, No. 3, July, 1901), Tunnicliffe and Rosenheim give the results of further metabolism researches upon the same children. In these experiments, which extended over twenty-eight days, the nitrogen deficits met with were—Child A, 27·58 grammes; Child B, 40·97 grammes.

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an excess of 39·3 grammes nitrogen in a three days' observation in one case, while in another of the same duration his deficit was 32·4 grammes.

Numerous researches, all quoted in our introduction, have been made, but for comparatively short periods continuously. Baginsky's figures alone are for children with acute nephritis on milk diet; we give them in full:

TABLE XIII.—*Daily loss or gain of nitrogen in Baginsky's metabolism experiments upon children with acute nephritis* (3A).

	A. (girl aged 13½).		B. (girl aged 13½).		C. (girl aged 5).	
	Daily loss or gain.	Progressive deficit.	Daily loss or gain.	Progressive deficit.	Daily loss or gain.	Progressive deficit.
1st day . . .	−3·043	3·043	+0·275	−0·275	−5·258	5·258
2nd day . .	−4·405	7·448	−2·280	2·005	−3·834	9·092
3rd day . . .	+0·090	7·358	−2·590	4·595	−4·638	13·730
4th day . . .	+2·467	4·891	−1·900	6·495	−4·679	18·409
5th day . . .	−3·724	8·615	−1·220	7·715	−5·350	23·759
6th day . . .	—	—	—	—	−0·831	24·590
Average daily loss	—	1·723 No gain of weight	—	1·543 No gain of weight	—	4·098 0·59 kg. gained.

− Means deficit. + Means surplus over intake.

No experiments upon children with nephritis have extended over a longer period. None have included a period of uræmia.

Our own results, both as regards the gain or loss of nitrogen each day and the progressive deficit from the beginning, are given in full in Table I.

The average deficit of nitrogen per diem was 0·506 gramme, which is much less than Baginsky found in his cases. An examination of the figures, in conjunction with the clinical account, shows that the deficit occurred almost entirely when the general condition of the patient appeared best. When uræmic symptoms were present, the output of nitrogen almost invariably exceeded the intake. This is very clearly illustrated by the curves in the chart.

Thus by the end of the tenth day the nitrogen deficit was 8·07 grammes; for the next twelve days the output exceeded

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the intake, so that on the twenty-second day the nitrogen deficit was only 2·48 grammes, and the patient had gained 1·1 kilos. in weight. While this recovery of nitrogen had been going on the patient was distinctly uræmic. On the twenty-third day his health improved greatly, and he continued better until the thirty-ninth day; during this time the nitrogen deficit increased to 23·75 grammes, and his weight to 1·5 kilos. more than at the beginning. During the last two days he became less well, and again excreted more nitrogen than he took as food, so that the deficit fell to 20·75 grammes. This was the commencement of a second uræmic period. Unfortunately we were unable to continue the work after March 31st, but we saw the patient the following week, and he was distinctly uræmic.

We had intended to compare the nitrogen deficit for the period (February 19th to March 6th inclusive) when baths were given with that of the remaining time without baths. The average daily deficit for the period of baths was 0·23 gramme nitrogen; for the period of no baths was 0·68 gramme nitrogen. At first sight this seems to show less loss of nitrogen by the skin when baths were given than without them, but the figures will not bear this interpretation for the following reasons:

1. The body-weight did not remain constant.

2. The amount of œdema was variable, and we had no means of measuring it exactly, and so determining how much of the variation in body-weight was due to water.

3. The period of uræmia supervened.

Tunnicliffe and Rosenheim (61A), in their experiments on two healthy children, found an average daily deficit of 0·75 and 0·64 gramme nitrogen. There were, it is true, gains of weight of 0·17 and 0·28 kilo. respectively, which, if entirely due to proteid, would account for part of the deficit.

Supposing that every 100 grammes of increased body-weight meant 3·3 grammes of food nitrogen converted into living tissues, there would still be 0·53 and 0·22 gramme nitrogen daily unaccounted for. We will compare these figures with our own. Over the whole experiment we found an average deficit of 0·50 gramme nitrogen daily.

This is less than the average figures in Tunnicliffe and Rosenheim's cases, if no account be taken of altered body-weight. In our case, the presence of a varying œdema vitiates

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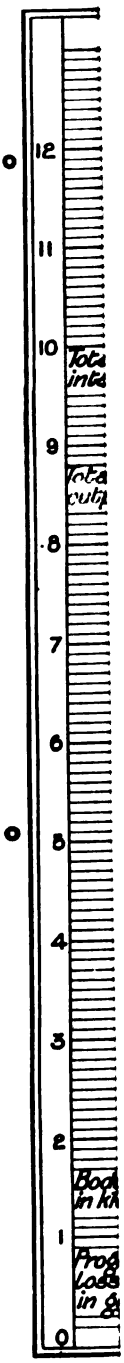

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allowances for changes in weight. An increase in our patient's weight was certainly not all due to building up of nitrogen into living proteid.

For example, at the end of the twenty-second day the total deficit was 2·484 grammes nitrogen; but the body-weight had increased by 0·85 kilo. If the latter were entirely due to proteid built up, it would contain 27·05 grammes nitrogen; so that 18·9 times our nitrogen deficit would be accounted for.

This is not probable. Even though we make no allowance for altered body-weight in our case, and yet concede that the gain in weight in the healthy children was entirely due to proteid, we find that our daily nitrogen deficit was less than Tunnicliffe and Rosenheim's in their longest experiment, though greater than that in their other. Remembering that our patient was covered with psoriasis, and that during the period when baths were given he often perspired very freely, whilst urea has been found in the sweat of uræmic patients (61), we expected our deficit to be greater.

The conclusions which we draw from this section of our work are therefore two, namely, that in our patient suffering from subacute nephritis—

1. The uræmic period was marked not by a retention of nitrogen, but by an output in the urine and fæces of more nitrogen than was taken in the food, the reverse being true when he was in better health.

2. The excretion of nitrogen by paths other than the kidney and bowel was not appreciably greater than it is in health.

Section X.

General conclusions.

Our general conclusions are, that in our patient with subacute parenchymatous nephritis—

1. The proportion of nitrogen excreted as urea was not less than that found in healthy persons, if the coagulable proteid in the urine be regarded as a foreign constituent, and not as a true excretory product.

If the coagulable proteid nitrogen be included, the proportion of urea nitrogen was less than in health.

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2. The above statements held good both for the uræmic and for the non-uræmic periods.

3. The uræmic period was marked by—

(*a*) An output of nitrogen in excess of the intake.

(*b*) A high, and almost constant ratio $\frac{\text{uric acid}}{\text{urea}}$.

4. The fæces nitrogen constituted a larger proportion of nitrogen output than has been found in healthy children on a milk diet.

5. The loss of nitrogen by other channels than the urine and fæces was not apparently greater than in health.

We desire to express our gratitude to Dr. Spriggs for his advice, and especially for his assistance during the illness of one of us. We thank Dr. Taylor and Dr. Fawcett for permission to investigate the case, Dr. Pembrey for the facilities he gave us in his laboratory, and the matron of Guy's Hospital, Sister Clinical, and her nurses, without whose hearty co-operation the work could not have been accomplished.

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May 7th, 1901.

23. *Chylous and chyliform ascites.*

By Robert Hutchison.

Opaque or opalescent effusions into the peritoneal cavity have been divided into two groups:

1. Chylous.
2. Pseudo-chylous, chyliform, or lactescent.

(1) Examples of the first group have been recognised for a long time, and are produced by the escape of chyle from the lacteals, receptaculum, or thoracic duct. The effusion closely resembles milk in appearance, and its opacity is due entirely to the presence of fat, of which it may contain from 1 up to 4 per cent., or even more.

The specimen exhibited was drawn off from the peritoneal cavity of a man aged 32, who was admitted to the London Hospital for ascites without other symptoms. It exactly resembled rich milk in appearance, and on standing a creamy layer formed on the surface, while a small quantity of pinkish clot separated out. It had a specific gravity of 1018, and under the microscope exhibited a number of highly refractile droplets.

On shaking up with potash and ether it became quite clear, and on evaporation of the ethereal solution a quantity of yellow fat was obtained (specimen exhibited). More exact analysis showed that the fat present amounted to 2·3 per cent.

Clinically such an effusion as this is usually associated with the presence of filariæ in the blood, but in this case these were not found, and the patient had never been abroad.

Anything which presses upon or obstructs the lacteals may also, however, be an efficient cause. The present case exhibited no other signs or symptoms, and when he passed from observation was apparently in good health.

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(2) The second group of effusions—those which are described as pseudo-chylous, chyliform, or lactescent—are of greater interest than the first, and have only been carefully investigated in recent years. The fluid in such cases is not so markedly opaque as in the first group, and has often a yellowish or greenish tint.

In other instances it closely resembles a weak solution of glycogen. Analysis shows that it contains mere traces of fat, much less than the amount (1·5 per cent.) which is required to produce opalescence.

The peculiar appearance of the fluid in these cases has been ascribed in some instances (1) to the presence of lecithin (of which 0·159 gramme per litre suffices to produce opalescence), in others to mucoid substances (2), and in a third and smaller group to the existence in the fluid of a proteid resembling casein (3).

The fluid, of which a specimen was shown, was obtained from the abdomen of a man aged 46, who was under treatment in the London Hospital for chronic nephritis. In the course of the disease ascites appeared, and he was tapped. The fluid obtained at the first few tappings was clear, but later on it became opalescent and of a slightly greenish colour. The patient eventually died, and at the *post-mortem* he was found to have subacute interstitial nephritis. The coils of intestines were matted, and the liver adherent to the under surface of the diaphragm, the condition being described by the pathologist as one of chronic purulent peritonitis. With the exception of the presence of a small amount of turbid fluid in the right pleural cavity the other organs were healthy.

The fluid in this case had a specific gravity of 1010, and showed under the microscope a number of minute refractile particles, some of them exhibiting Brownian movement.

When shaken up with potash and ether the fluid remained quite opalescent, and on evaporation of the ether a mere trace of fat was obtained. The acrolein test was also negative. Acetic acid produced no precipitate in the original fluid.

On dialysis a copious sediment was thrown down, and the fluid became clear. This sediment was only partly soluble in normal saline, the solution being quite transparent. The residue dissolved in stronger salt solution, forming an opalescent fluid,

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from which acetic acid threw down a copious precipitate. The precipitate was exhausted with hot alcohol and ether. After evaporation and incineration the alcohol and ether extract was found to contain no phosphorus, showing the absence of lecithin. The residue, which was insoluble in alcohol and ether, was also incinerated, and yielded, on examination, a small amount of phosphorus. Some of the original fluid was digested for some days with pepsin and hydrochloric acid. A precipitate was thrown down, purified with alcohol and ether, and incinerated. It gave a fair yield of phosphorus, but not enough to permit of exact quantitative estimation, nor was one able to examine it for nuclein bases.

Direct examination of the original fluid for lecithin by extraction with alcohol also yielded a negative result, and hydrolysis with a dilute mineral acid gave no reducing body.

These experiments show, I think, that the opalescence of the fluid in this case was not due to lecithin or mucoid substances, but that it must be ascribed to some form of nuclein or paranuclein containing proteid, probably derived from cellular disintegration; the fluid would accordingly come under the third of the varieties described above.

It may be added, in conclusion, that such fluids have no special clinical significance, as they may be met with in very various pathological conditions.

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2. *Hammarsten.*—"Ueber das Vorkommen von Mukoid-Substanzen in Ascites-Flüssigkeiten," 'Zeit. f. physiol. Chemie,' 15, 20e, 1891.
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Rendu.—'Journ. des Practiciens,' March 16th, 1900.

For further references see—

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Rotmann.—'Zeit. f. klin. Med.,' xxxi, 1897, p. 416, gives extensive references to clinical cases.

March 4th, 1902.

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24. *On a brown pigment in the urine.*

By F. H. Thiele.

During the past year there have been four cases at University College Hospital of patients whose urine contained a brown pigment which does not conform to any of the described pigments.

The cases in which this pigment occurred were:

1. A middle-aged woman suffering from pyorrhœa alveolaris. The patient was admitted in an exhausted condition and only lived a few days. Whilst in the hospital she passed a urine which had a greenish-brown colour. The urine yielded no spectroscopic band before or after the addition of an acid; it also contained no bile pigment, neither did it give reactions conforming to any known pigment. On *post-mortem* examination the organs presented marked fatty changes.

2. A middle-aged woman suffering from a subacute septic condition and subsequently developing parotitis. Her urine on admission presented similar characters, but a few days after admission the urine yielded the characteristic urobilin band which it previously did not possess. The patient had a slight yellowish tinge, and on her abdomen there was a raw surface produced by a blister; the edges of this surface were coloured a marked green.

3. A boy aged 5 years suffering from appendicitis. The urine of this child was of a pale greenish-yellow colour for several days; it also did not give evidence of any described pigment. The urine at no time gave a urobilin band.

4. A woman of about thirty years of age suffering from a peculiar sloughing ulceration in the vagina. In this case the woman periodically passed this peculiar urine, the alteration in the urine being accompanied by a rise of temperature. The urine at first passed was of a greenish-brown colour, but subsequently was simply brown. In this case again the urine yielded no characteristic reaction. In the intervals of passing this urine a urobilin band was never detected.

From the greenish-brown urine there was precipitated in addition to the brown pigment—which was completely soluble

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in acidulated alcohol—other pigments which were insoluble in alcohol, chloroform, or ether, but which yielded a yellow pigment soluble in water, and another grey one insoluble in water. When the urine was simply brownish in colour the brown pigment alone was obtained.

The brown pigment is precipitated from the urine by ammonium sulphate, lead acetate, and milk of lime. It is not precipitated by ammonium chloride and non-alkaline solution of barium chloride, but is nearly insoluble in alkaline solution of barium chloride. The pigment is freely soluble in acidulated alcohol, less freely in alcohol alone, or water; it is easily soluble in amylic alcohol, less so in chloroform, and quite insoluble in ether. On evaporation it yields a dark brown amorphous powder which is not deliquescent. Repeated evaporation of the acidulated alcoholic solution renders the pigment darker in colour and less soluble than before.

The acidulated alcoholic solution when concentrated is reddish brown in colour, and in dilute solution is amber-coloured, not having the reddish tinge that urobilin has. On the addition of an alkali the solution turns yellow.

The pigment has no spectroscopic band. In concentrated solution it blots out the spectrum from the red onwards, and as the solution is diluted this gradually fades, and never at any time is there a definite band. The specimens have now been kept for a long period both in the dark and in the sunlight, and no change has occurred in them.

On the addition of ammonia and zinc chloride there is no fluorescence, neither is there any spectroscopic change. An alkaline solution of the pigment in caustic soda does not yield on the addition of calomel the rose-red solution obtained under similar conditions with urobilin, but the colour remains unchanged. When copper sulphate is added to a solution of the pigment in a caustic alkali there is no change of colour corresponding to the "biuret" obtained when urobilin is similarly treated.

A solution of the pigment treated with tin and hydrochloric acid becomes bleached, a similar result being obtained with peroxide of hydrogen. When the pigment is treated with nitric acid to which are added a few drops of fuming nitric acid it is rapidly bleached, more so than by the previously mentioned

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methods. Bromine water when added to a solution of the pigment gives a whitish precipitate and the solution becomes decolourised.

Potassium permanganate produces no change in the colour of a solution of the pigment, neither is there any spectroscopic change.

A solution of this pigment was next made in absolute alcohol, the pigment having been purified by a repeated precipitation with ammonium sulphate. On adding aldehyde to this solution in the sunlight and gently heating no spectroscopic change occurred, whereas a pure solution of urochrome at the same time by this treatment developed characteristic spectroscopic changes.

Inoculation of an alkaline solution of this pigment with fæcal micro-organisms in broth did not produce any alteration in the pigment, there being no signs of urobilin or urobilinogen in the broth.

In Case 2 the fæces gave distinct evidence of urobilin during the time the patient was passing the above-described urine. It will thus be seen that the pigment agrees with urobilin in many of its properties, but differs in two marked particulars, viz. in the absence of spectroscopic bands and the green fluorescence with zinc chloride and ammonia. It is apparently not urobilin excreted in a somewhat altered state, which gives spectroscopic band after standing some time. From the failure of aldehyde to produce in it the spectroscopic bands produced with urochrome, it follows that the pigment is not urochrome. In Case 2 the simultaneous presence of the yellow pigmentation of the skin and the green coloration of the edges of the raw abdominal area, together with the occurrence of this brown pigment followed by urobilin, is highly interesting. *March 4th*, 1902.

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25. *An undescribed purple pigment in urine.*

By H. A. Schölberg.

The urinary pigment to be described was found in the urine of a man aged 28, who was admitted, suffering from peripheral

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neuritis, to St. Bartholomew's Hospital. Dr. Ormerod, under whose care the patient had been for some months, has kindly allowed this communication to be made. (For diagnosis of this case see 'Clin. Soc. Trans.,' vol. xxxv, 1902.) During the time the patient has been under observation he has always passed urine containing the chromogen of the pigment. The abnormality is almost certainly congenital, for it has been noticed since early childhood; his father and the patient's sister immediately preceding him in point of age pass urine containing the same pigment or rather chromogen, though in their case the amount is less. The patient has noticed that the amount of chromogen is increased when he is feverish, and this has been confirmed while he has been under observation, the urine becoming much darker on standing than when the temperature is normal. These facts exclude the possibility of the condition being due to any drug that the patient may have taken. The condition is probably an individual variation of no pathological significance, and is put on record to prevent such a urinary anomaly from being credited as due to an associated disease. The output of urine is normal in amount; sp. gr. 1020, no albumen, no sugar. Of natural colour when just passed, it rapidly darkens on exposure to air and light, becoming at the end of twenty-four hours of a deep purple-black colour.

Method of extraction of the pigment.—Precipitation with baryta mixture affords the best means of extraction, the barium sulphate carrying the pigment down mechanically, and settling as a pinkish coloured powder. The urine, which is of a faint pink colour when filtered, becomes on standing as deep in colour as the original urine, showing that the chromogen and pigment are present at the same time; the process may be repeated by adding soluble sulphates and again precipitating with baryta, but the filtered urine will again darken on standing at the end of a few days. The barium sulphate yields up the pigment sparingly to all solvents; dilute solutions of acids or alkalies take up the pigment to a certain degree; acid alcohol and acid chloroform, separately or mixed, to a less extent. Whatever the solvent used may be, it always darkens on standing, showing that a portion of the chromogen has been precipitated with the $BaSO_4$ and remained unchanged. Other solvents, such as ether, ethyl acetate, acetone, benzene, nitro-benzene, ligroïn, do not dissolve

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the pigment or chromogen to any appreciable extent. Direct extraction from the urine is not possible.

Physical properties.

1. Light increases the rate of formation of the pigment. The fresh urine placed in a Büchner tube (anaërobic) and exposed to light shows a depth of colour not found in a similar tube kept in the dark.

2. Exposure to the air increases the rate of colour formation, the increased effect of light not being appreciable.

3. Heating the urine when just voided at once causes the urine to develop the characteristic colour.

Chemical properties.

1. The pigment is very stable; it will, in part, pass into solution on adding strong sulphuric acid to the barium sulphate precipitate, and show the same spectroscopic character on dilution. The addition of alkalies to neutralise or make alkaline turns the solution a brownish colour, but no precipitate results. On acidifying the original colour is restored.

2. The insolubility of the pigment has already been referred to, and this has prevented the isolation of the pigment in any degree of purity or in appreciable amount.

3. Reduction with zinc-dust and acetic acid decolourises the pigment, and on adding an oxidising reagent, after filtering, the colour is restored and gives the same absorption spectrum.

4. Acetylation yields on throwing into water or on adding chloroform to the filtrate a white opalescence which yields the same pigment on decomposition by boiling with acids.

5. A portion of the impure pigment was tested for iron with a negative result.

Spectroscopic characters.

1. The urine when passed is of natural colour and shows no definite absorption band, but on gently heating an ill-defined band appears at the junction of the green and blue of the spectrum, gradually absorbing the whole of the blue end of the spectrum with the development of the colour. The boiled urine, further, gives a very faint band of alkaline hæmatoporphyrin. The father's urine gives the same result spectroscopically.

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2. Acid alcohol solutions give a faint spectrum of acid hæmatoporphyrin as well as the absorption peculiar to the pigment.

Differentiation of the pigment from other previously described purple pigments.

1. The purple pigment described by Dr. Garrod ('Clin. Soc. Trans.,' vol. xxxiv) is distinguished by the fact that that pigment is easily extracted by the method he has introduced for the extraction of urochrome;[1] no such result follows in this case.

2. The purple pigment referred to by Leube is readily extracted from the urine by the direct addition of ether.

3. From uro-rosein and the indigo pigments it is different in its spectroscopic and other properties.

4. It is not alkaptonuria—not reducing Fehling's solution or giving the benzoyl derivative after treatment by the Schotten-Baumann reaction.

5. The pigment is a familial anomaly.

Conclusions.—The pigment has not been obtained pure or in quantity, but nevertheless the category in which it should be placed is clear. As in pathological hæmatoporphyrinuria the colour of the urine is due to the associated purple pigment, so in this case the hæmatoporphyrinuria occurring in this family is associated with an allied pigment, similar in colour but having different chemical characters.

Lastly, I would thank Dr. A. E. Garrod for his help and advice; without his direction the matter could not have been investigated by me. *March 4th*, 1902.

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26. *A case of phlegmonous gastritis from streptococcus infection.*

By W. Cayley.

The patient was a woman, aged 26, a domestic servant. She was admitted into the Middlesex Hospital on November 19th, and died on November 21st.

Her previous health had been good, and she could assign no cause for her illness.

[1] 'Proc. Roy. Soc.,' vol. lv, 1894.

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On November 13th she was attacked by cold shivers, slight sore-throat, severe headache, and pains in the abdomen and limbs. She continued her work till November 18th, when she took to her bed. On the 17th she began to vomit, and on the 18th the vomiting was very severe and accompanied by great abdominal pain. The bowels had been constipated, and she took a dose of castor oil, which was followed by some dark offensive motions.

She was admitted into the hospital on the afternoon of the 19th. She was a pale anæmic woman with dark rings round the eyes; she complained of severe abdominal pain, and also of pain in the limbs. Pulse was 132, respirations 36, temperature 104·6°. Her tongue was very red, with a dark brown strip round the centre. The abdomen was somewhat distended, especially in the epigastric region, and was tender on palpation. Area of stomach resonance appeared considerably increased. Nothing abnormal was visible in the fauces. A rose-coloured spot was observed in the right iliac region; urine free from albumen, and did not give Ehrlich's reaction. The blood was examined for Widal's reaction, but, as was ascertained after the death of the patient, the result was negative.

When I saw her the next day she presented all the characters of acute septic peritonitis. She lay on her back with her knees drawn up, her abdomen was greatly distended and motionless, and very tender. This great distension had come on since the early morning, and was most marked in the upper region. The tympanitic resonance extended as high as the nipples, and the heart and liver were displaced upwards, but a narrow space of hepatic dulness was perceptible about the level of the right nipple. Her general condition was that of collapse; her tongue was dry and brown, pulse very small, the temperature had fallen to 101·2°. There had been no vomiting or action of the bowels since her admission.

The patient was evidently suffering from peritonitis with distension of the stomach. This at the time I erroneously considered to be the effect of the peritonitis. The cause of the peritonitis was not apparent, in the absence of any distinctive indications of perforation, and considering the collapsed condition of the patient I did not think any exploratory operation advisable. She gradually sank and died the next day.

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The *post-mortem* examination was made by Dr. Campbell Thomson, and Mr. Foulerton kindly conducted the bacteriological examination.

The body was well nourished and the rigor mortis pronounced. There was general purulent peritonitis. The stomach was considerably dilated, its coats were thickened; the serous covering like the rest of the peritoneum was injected. On incision the submucous and, to a less extent, the muscular and subserous coats were found infiltrated with pus; the mucous membrane appeared intact. This change was most marked over the pyloric third of the stomach. The intestines appeared normal; nothing abnormal was found in the rest of the body.

Bacteriological examination.—Stained cover-glass specimens made from the purulent exudation of the submucous coat of the stomach showed a number of bacilli which did not stain by Gram's method, and which resembled morphologically *B. coli communis*. There are also present a few short chains of streptococci which stained by Gram's method.

Culture tubes were inoculated from the spleen juice, and from the purulent exudation in the submucous coat of the stomach. The tubes inoculated from the spleen juice remained sterile, except from an accidental contamination. From the purulent exudation a pure culture of *B. coli communis* was obtained. The streptococcus seen in the exudation not being recovered in culture, I suppose the streptococcus infection may be regarded as primary, and that of the *B. coli communis* as a secondary effect.

A large number of cases of phlegmonous gastritis have now been recorded. In vol. iv of the 'Edinburgh Hospital Reports' Dr. Leith has collected fifty-two cases, and several have been published since, but the pathology remains somewhat obscure. Two conditions would appear to be necessary to produce the affection. First, the presence of virulent pyogenic organisms; secondly, some impaired nutrition of the mucous membrane of the stomach, so as to allow them to penetrate.

With regard to this second cause it is remarkable how large a number of the patients were of intemperate habits, and how often the attack followed some excess or error of diet. By these the protective epithelium of the stomach might be temporarily or permanently injured. It has, also, in several cases

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followed mechanical or other injuries to the stomach. In a well-known case reported by Dr. Kelynack in the 'Lancet' of 1896, the attack occurred in chronic ulceration and stricture of the lower part of the œsophagus with burrowing sinuses, the result of corrosion by oil of turpentine. It has also followed both cancerous and simple ulceration. In one case the attack was caused by pressure of the corner of a table on the epigastrium, in another from a blow on the epigastrium. It has also followed the operation of gastrostomy.[1] It has been met with in cases of general pyæmia, where possibly the microbes were conveyed to the stomach through the circulation.

As to the origin of the virulent germs nothing definite is known. It seems unlikely that they could be conveyed by the food. A possible source might be suppuration connected with the teeth.

With regard to the diagnosis, I am not aware that any fatal case has been diagnosed during life. Dr. Dörbeck claims to have diagnosed a case which recovered. The patient, after an error in diet, was attacked by epigastric pain, high fever, and vomiting, and pus was present in the vomit. She recovered, but seven months afterwards the stomach was still in a highly irritable condition.

Where, as in my case, the mucous membrane is intact, vomiting of pus could hardly occur, but in many cases the mucous membrane has been found riddled by small perforations leading to the infiltrated submucous layer.

The characteristic symptoms which might be expected would be epigastric pain and tenderness, dilatation of the stomach, vomiting with the presence of pus in the vomit, high fever, and the supervention of general peritonitis. But in several cases there has been a complete absence of gastric symptoms during life, and the condition has been unexpectedly found on *post-mortem* examination. In my case the patient did not vomit while under observation, but probably the vomit would have furnished no indications. *January 21st*, 1902.

[1] Case reported by Mr. Quarry Silcock, 'Path. Soc. Trans.,' vol. xxxiv, p. 90.

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27. *Pneumococcic gastritis, with some remarks on the infection of mucous membranes by* Diplococcus pneumoniæ.

By Alexander G. R. Foulerton.

[With Plate VIII.]

Pneumococcic lesions of mucous membranes have attracted comparatively little attention from pathologists, partly because their importance has been overshadowed to some extent by other more conspicuous results of pneumococcic infection—such as pneumonia, peritonitis, meningitis, and arthritis; and partly because of some technical difficulty in the isolation of this particular organism when it occurs in lesions of mucous surfaces, which will frequently be so contaminated with other bacteria that the primary causative agent may be difficult of identification. A considerable number of writers have, however, referred more or less casually to various morbid conditions of mucous membranes, such as laryngitis and enteritis, occurring in fatal cases of pneumonia; and it is probable that pneumococcic lesions of mucous membranes are of much more frequent occurrence than the number of recorded cases in which a satisfactory bacteriological examination has been made would indicate.

The case of acute membranous gastritis due to pneumococcic infection which will be next referred to is of interest as being, so far as I can ascertain, the first case of the sort recorded.

The patient, aged 26 years, was admitted into Dr. W. Pasteur's wards at the Middlesex Hospital under the care of Dr. F. J. Wethered; and I have to thank both these gentlemen for their permission to make use of the clinical notes of the case. The patient was admitted on December 27th, and the following history was obtained:—A fortnight previously he came under treatment for a "quinsy," and had remained ill ever since. Three days before admission a free attack of epistaxis came on whilst he was blowing his nose, and since then there had been an almost continuous oozing of blood from the nostrils. On the day before his admission he had brought up by the mouth a quantity of dark-coloured matter which had a very disagreeable smell. On admission the patient was anæmic to an extreme degree. His

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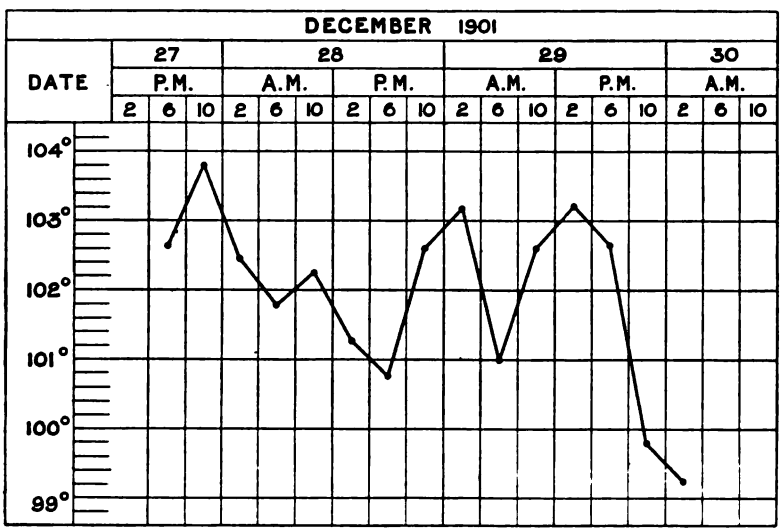
lips were swollen, and in the skin of the back, around the lips, and on the cheeks there were a number of petechial hæmorrhages. There was coagulated blood in the nostrils, on the lips, and on the gums round the teeth. The breath was very offensive, and the tongue was dry and covered by a dark grey fur. The pulse was frequent, small, and soft. On the 28th the oozing of blood from the nostrils continued, and no further change of any importance in the symptoms was noted. On the 29th the patient was restless, the respiration rate was hurried, and the pulse was frequent, very small, and of low tension. The temperature began to fall towards the evening, and the



Temperature chart of the case whilst under observation.

patient died early the next morning with signs of urgent dyspnœa. It must be noted that throughout the illness there had been no indications in the way of local pain or vomiting which would have suggested any gastric disturbance.

The examination of the body was made about seven hours after death on a cold day. Rigor mortis was present, and the body appeared to be well nourished generally. The skin had a blanched appearance, and there were numerous petechial hæmorrhages scattered over its surface; there were several "mulberry spots" on the chin and on the cheeks. There was a

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deepish, ragged ulcer in the right tonsil, and a large blood-clot occupied the upper part of the pharynx. The œsophagus was of natural appearance. The stomach was of normal size, and contained some dark-coloured fluid matter which had an extremely offensive "cheesy" smell. The viscus was lined from end to end with a roughish exudation membrane, which towards the cardiac extremity was of an almost black colour and was intimately attached to the underlying mucous membrane, and towards the pylorus was of a greyish colour and less closely attached, so that here it could be peeled off in small flakes from the mucous membrane underneath, in which there were numerous petechial hæmorrhages. The rugæ of the stomach were swollen, and stood out prominently. The wall of the stomach as a whole was slightly thickened, but the increase appeared to be due mainly to the new membranous formation. The exudation membrane terminated abruptly at the cardiac and pyloric openings. The general appearance of the stomach was striking, and bore some superficial resemblance to what is seen in a severe case of poisoning by a mineral acid. The serous coat of the stomach was somewhat congested, and the peritoneal sac contained a few ounces of slightly turbid fluid. There were small petechial hæmorrhages on the pulmonary pleuræ, on the epicardium, and on the surface of the liver and kidneys. There was an interstitial hæmorrhage, of an area of about the size of a shilling piece, close to the surface of the right lung, and a small excess of blood-stained fluid in the pericardial sac. Beyond these lesions nothing of importance was noted at the examination.

Bacteriological examination.—Various culture tubes were inoculated (1) from the spleen juice, (2) from the blood of the femoral vein, (3) from the substance of the exudation membrane on the surface of the stomach, (4) from the juice of the hæmorrhagic area in the right lung, and (5) from the juice of one of the "mulberry spots" on the face. From the blood of the femoral vein, from the mulberry spot, and from the hæmorrhagic area in the lung pure cultures of *Diplococcus pneumoniæ* were obtained. From the tubes inoculated from the exudation membrane from the stomach two species of bacteria were isolated—*Diplococcus pneumoniæ* and a bacillus which, in its cultural characteristics, corresponded generally with *Bacillus mesenteri-*

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EXPLANATION OF PLATE VIII,

Illustrating Mr. A. G. R. Foulerton's communication on Pneumococcic Gastritis. (Page 286.)

The stomach viewed from the inner aspect, showing the layer of necrosed tissue and exudate covering the surface. Slightly reduced from a photograph.

[On the right-hand border a square piece has been cut away for histological investigation.]

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cus vulgatus. From the spleen a growth of a bacillus corresponding with the last was obtained, and *Diplococcus pneumoniæ* was not isolated from this organ. In sections made through the substance of one of the "mulberry spots," and stained for bacteriological examination, no bacteria of any sort could be found. In sections made through the coats of the stomach and the overlying false membrane, two kinds of bacteria could be recognised. There were considerable numbers of bacilli, which were probably of the same species as that isolated in culture, and also a number of cocci arranged in isolated pairs and in small colonies, which, stained by Gram's method, showed a distinct tendency to diplococcal arrangement, were in many cases surrounded by a distinct capsule, and in all respects corresponded with *Diplococcus pneumoniæ* as it is seen in animal tissues. These bacteria were seen principally in the exudation membrane, and in the immediately subjacent necrotic tissue; only a few could be found in the submucous connective tissue, and then only just below the muscularis mucosæ.

The strain of *Diplococcus pneumoniæ* isolated was of comparatively low virulence for rabbits: two animals received by intra-peritoneal injection medium doses of a forty-eight hours old culture in broth, and recovered after a temporary illness.

General histological examination.—In sections through the wall of the stomach it was seen that the changes chiefly affected the glandular structure of the mucous membrane. On the surface there was a fibrinous layer of considerable thickness, beneath which the glandular layer of the mucous membrane had undergone an extensive necrosis, in some places down to the muscularis mucosæ, so that frequently no recognisable trace of tubular structure remained. In other places the deeper portions of the glands retained their general structure, but the lining epithelium was cloudy or disorganised. Small masses of altered blood-pigment were scattered throughout the mucous membrane, and quantities of apparently unaltered red blood-cells could be seen lying both within the lumen of the glands, and free in the interglandular connective tissue. Below the muscularis mucosæ the submucous connective-tissue layer appeared to be but slightly thickened; the spaces of the connective tissue were somewhat enlarged, as if after distension by a serous effusion; and there were largish masses of homogeneous yellowish-brown

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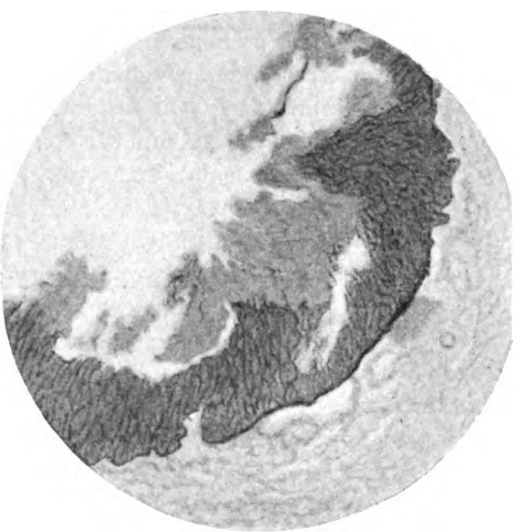
pigment scattered about, especially in the neighbourhood of blood-vessels. The muscular coat showed very little change; here and there were masses of altered blood-pigment resembling that seen in the submucous layer. One notable point in the histological examination was the very slight evidence of any inflammatory reaction. In the submucous coat there was no indication at all of such reaction, and in the muscular coat there were only a few collections of leucocytes at wide intervals.

A consideration of the pathology of the case suggests that the primary lesion was perhaps a pneumococcic infection of the

FIG. 21.



A microscopic section of the gastric mucosa, showing the necrosis of tissue and superjacent fibrinous exudate. (Drawn by Leslie Milburn.)

right tonsil, though this was not proved. The infection of the stomach then resulted from the swallowing of the parasite, and the general infection followed the invasion of the stomach. The healthy stomach, with its strongly acid secretion, would in all probability be an extremely unfavourable site for the growth of *Diplococcus pneumoniæ*, and it is not unlikely that a certain amount of gastritis resulting from the swallowing of fœtid pus from the ulcer on the tonsil was a necessary preliminary to the pneumococcic invasion of the gastric mucous membrane.

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The absence during life of any vomiting is noteworthy, the more especially as there was no indication after death of any distension of the viscus, which would have suggested paralysis of the muscular coat.

The pathological changes in the stomach in this case form a strong contrast to those in the case of phlegmonous gastritis due to streptococcic infection described by Dr. Cayley,[1] in which, whilst the surface epithelium and glandular layer of the mucous membrane were hardly at all affected, there was great thickening of the submucous connective-tissue coat, the result of a purulent infiltration. I have said that I have not been able to find any previous record of a case of this sort, but Dieulafoy, in a lecture on "Gastrite Ulcéreuse Pneumococcique,"[2] has described a condition which is probably a later stage of a similar lesion. Dieulafoy's case was that of a man aged 35 years, who was admitted into hospital with a history of pain in the side for seven days past. On admission, a diagnosis of pneumonia on the right side was arrived at, but there was also very marked abdominal symptoms in the way of pain, diarrhœa, and vomiting. Two days after admission there was a severe attack of hæmatemesis, followed by the appearance of blood in the stools, and again hæmatemesis; the patient died on the fourth day after admission. At the examination after death evidence of a general pneumococcic infection was found, pneumonia on the right side, pericarditis, and peritonitis; the specific coccus was isolated from all these lesions. On opening the stomach it was seen that the mucous membrane presented a number of small erosions, either round or oval in shape, and with a diameter of from 2 to 3 mm. The erosions were especially numerous near the pylorus, and as many as ten or twelve could be counted in a square centimetre of the mucous surface; many of them had a small blood-clot at their base. Dieulafoy describes the lesions in his case as consisting of an erosion of the whole thickness of the glandular layer of the mucous membrane down to the muscularis mucosæ, due to a rapid and localised necrosis of the areas affected. There was little or no inflammatory reaction in the

[1] Cayley, "A Case of Phlegmonous Gastritis due to Streptococcic Infection," 'Transactions of the Pathological Society of London,' vol. liii, 1902.

[2] Dieulafoy, "Gastrite Ulcéreuse Pneumococcique, grandes Hématémèses," 'Clinique Médicale de l'Hôtel Dieu de Paris,' iii, p. 219, 1898–9.

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tissues in the neighbourhood of the erosions. In sections a large number of diplococci could be seen both in the interglandular connective tissue and within the capillaries, the distribution of the cocci being general and not limited to the immediate neighbourhood of the erosions.

It is extremely probable, then, that Dieulafoy's case simply represents a later stage of a lesion such as was found in the case which I have described; in the latter case, if the patient had lived long enough for the exudation membrane and the necrosed portions of the mucous membrane to be thrown off, it is probable that a condition of ulceration similar to that which Dieulafoy describes, but perhaps on a rather larger scale, would have resulted.

Dieulafoy also refers to another condition of the stomach occurring in the course of a pneumococcic infection. The patient, a man aged 45 years, was admitted into hospital with signs of pneumonia on the left side; subsequently there were indications of peritonitis and an acute arthritis of the left wrist. At the examination after death the diagnosis of pneumonia was verified; there were three interlobular abscesses in connection with the left lung, purulent meningitis, peritonitis, suppurative arthritis of the left radio-carpal joint, and vegetations on one of the aortic valves. The presence of *Diplococcus pneumoniæ* was demonstrated in these lesions. On opening the stomach a number of hæmorrhagic patches were seen in the mucous membrane and in the submucous connective tissue. In the mucous membrane these hæmorrhagic patches were situated just below the surface, and there was no sign of inflammatory reaction around them. Bacteriological examination of the wall of the stomach gave no results.

This second case referred to by Dieulafoy probably represents a different condition of things from that prevailing in his first case and in my own. In the two latter cases there is the result of a local infection of the mucous membrane from without by swallowing; in the other the change is probably merely one of the general effects of a pneumococcic blood infection in which, whether occurring naturally in man or induced artificially in experimental animals, there are to be found sometimes petechial hæmorrhages into the skin and the mucous and serous membranes.

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Apparently closely allied in its pathology to the ulceration of the stomach described by Dieulafoy is the case of ulceration of the colon recorded by Rathery and Chauffard.[1] The patient was a man aged 51 years, who was admitted into hospital with pneumonia at the right base. After admission there were three attacks of profuse hæmorrhage from the bowel, and the patient died on the thirteenth day of his illness. At the examination after death a double pneumonia was found. The mucous membrane of the ascending colon was coated with blood, and there were blood-clots in the transverse and descending portions. Scattered over the mucous membrane were punctiform hæmorrhages, and at the junction of the transverse and descending portions there were five or six superficial ulcers, each with a diameter of from one to two millimètres. There were similar ulcers at the lower end of the colon and one in the rectum. These ulcers had resulted from a destruction of the glandular layer of the mucous membrane, the muscularis mucosæ not being affected. *Diplococcus pneumoniæ* was isolated from the blood and from the pneumonic portions of lung, and in sections through the ulcers in the colon there could be seen diplococci which stained by Gram's method.

With regard to other mucous membranes, pneumococcic lesions of practically every such surface have been described and verified bacteriologically.

In addition to causing acute abscess of the tonsil *Diplococcus pneumoniæ* appears to be a fairly frequent cause of acute membranous tonsillitis and pharyngitis. The exact bacteriological identification in these cases is rendered difficult by the fact that the organism is a frequent parasite of the healthy mouth. But the number of cases in which there are the formation of a false membrane and destruction of the superficial layer of the epithelial membrane associated with the presence of the coccus in predominant numbers, and without any of the other bacteria —*Bacillus diphtheriæ*, *Streptococcus pyogenes*, and *Saccharomyces albicans*—which are known to cause similar lesions, leaves little doubt as to the fairly frequent occurrence of an acute membranous pharyngitis due to this cause. Bezançon

[1] Rathery and Chauffard, "Hémorragie Intestinale mortelle dans un cas de Pneumonie," 'Bulletin de la Société Médicale des Hôpitaux,' 3me série, 1901, p. 976.

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and Griffon, who have especially studied this class of cases, have tested the serum reaction in ten cases of acute non-diphtheritic pharyngitis.[1] Employing the method which they have devised for testing the serum reaction in pneumococcic infection, these writers claim to have obtained a positive agglutinative reaction with cultures of *Diplococcus pneumoniæ* in every case.[2]

Amongst the consequences of pneumococcic pharyngitis is perforation of the pillars of the fauces, as in a case recorded by Munro.[3] In this case there was a membranous tonsillitis which spread over the palate from one side to the other, and *Diplococcus pneumoniæ* was present in six out of seven examinations made. During the case some nerve symptoms were observed which were thought to be suggestive of diphtheria, but which were probably an example of the paralysis which has been observed on a few occasions as a sequela of pneumococcic infection.

Another possible result of pneumococcic pharyngeal infection, spreading along the Eustachian tube, is the otitis media which is not infrequently caused by this organism.

I have also examined a single case of laryngitis probably due to this organism, and occurring in a man who died with a pneumococcic abscess of the lung. On one of the false vocal cords there was a greyish membrane which was closely adherent to the underlying surface. *Diplococcus pneumoniæ* was isolated in pure culture from the pulmonary lesion, and diplococci resembling it were seen in smear preparations made from the laryngeal membrane.

In connection with the eye there is a form of membranous conjunctivitis caused by the coccus, sometimes occurring without any obvious source of auto-infection, sometimes in the course of a pneumonia, and then probably caused by direct conveyance of infection. This membranous pneumococcic conjunctivitis is probably not so common as a more localised suppurative keratitis

[1] Bezançon and Griffon, "Le Pneumocoque dans les Angines," 'La Presse Médicale,' 1900, p. 294.

[2] "Étude de la Réaction agglutinante du sérum dans les Infections expérimentales et humaines à pneumocoques," 'Annales de l'Institut Pasteur,' tome xiv, p. 449, 1900.

[3] Munro, "Membranous Sore-throat and Perforation of the Faucial Pillars resulting from Infection by the Pneumococcus," 'Glasgow Medical Journal,' vol. lvi, p. 274, 1901.

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due to the same cause which has been described by several writers. Uhthoff, for instance, out of fifty cases of suppurative keratitis found *Diplococcus pneumoniæ* in pure culture twenty-four times, and associated with other bacteria seven times.

Diplococcus pneumoniæ does not seem to have been often found by those who have specially studied the bacteriology of the uterus and vagina, whether healthy or diseased. Doyen states that he has identified the coccus in the secretion of the healthy vagina, but I cannot find any record of its occurrence in cases of vaginitis. Cohn[1] has recorded a case of pneumococcic endometritis and general infection in a woman aged 35 years, who was admitted into hospital with metrostaxis coming on three months after a miscarriage. After death there were found suppurative endometritis with retained portions of placenta, ulcerative endocarditis affecting the aortic valves, suppurative meningitis, and two softening infarcts in the spleen. *Diplococcus pneumoniæ* was present in all the lesions.

With regard to pneumococcic salpingitis there is rather more evidence; Witte identified the coccus in four out of thirty-nine cases examined, Hartman and Morax found it in two out of thirty-three cases, and other cases have been published.

Infection by the vagina has been thought to explain the sex-incidence of pneumococcic peritonitis; but as a matter of fact the significance of available statistics on this point is not quite clear. It is true that a large majority of the cases recorded in children have happened in girls; but, on the other hand, the few cases which I have been able to find recorded in adults, and occurring otherwise than as an incident of a general infection, have all been in males.

The last case of pneumococcic infection of the mucous membranes which need be mentioned is the rather remarkable one published by Cary and Lyons[2] of a boy, aged 11 years, who, with an attack of acute lobar pneumonia, developed on all the mucous surfaces of the body open to inspection a pseudo-membranous exudation caused by *Diplococcus pneumoniæ*. The boy's illness began on January 5th with sore throat and pyrexia.

[1] Cohn, 'Münchener medicinische Wochenschrift,' 1899, p. 1558.

[2] Cary and Lyons, "Pseudo-membranous Inflammation of the Mucous Membranes caused by the Pneumococcus," 'American Journal of the Medical Sciences,' vol. cxxii, p. 298, 1901.

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On the 7th there were indications of lobar pneumonia and an abundant white exudation membrane was noticed on the tonsils. This exudation membrane spread to the general cavity of the mouth and to the gums; it could be peeled off in shreds, leaving beneath a raw, granular, bleeding surface. Four days later a fibrinous conjunctivitis with numerous subconjunctival hæmorrhages developed. Two days later again the glans penis—the organ had been circumcised—became covered by a thick, adherent membrane. On the day next following, mucus was found in considerable quantities in the stools, and a deposit of false membrane formed round the anus. The patient ultimately recovered. *Diplococcus pneumoniæ* was present in the septum, and was identified in all the various exudation membranes; pure cultures were isolated and tested on rabbits in the usual way.

A consideration of these manifestations of pneumococcic infection in mucous membranes generally shows that here the pathogenic action of the coccus, after allowing for different local conditions, may be much the same as when it causes a lobar pneumonia. There are the same fibrinous exudation and destruction of surface structure and the same tendency to extravasation of blood that are seen when the pulmonary vesicles are attacked. *January 21st*, 1902.

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28. DISCUSSION ON LYMPHADENOMA IN ITS RELATION TO TUBERCULOSIS.

(*December 3rd*, 1901.)

[With Plate IX.]

HENRY T. BUTLIN.

MR. PRESIDENT, it is such a long time since I came here to take part in any serious debate that I scarcely dare to do so now, because really pathology has altered so much, even since the time when I was in that chair, sir, and the terms of it are so very different from those with which I was acquainted many years ago, that I feel I am not fit to cope with it. Yet, when it was suggested to me some few weeks ago that I should open a discussion on the relation of lymphadenoma to tubercle, I accepted without the least hesitation, because I was quite sure that there would be nobody in this room who was likely to be more ignorant on the subject than I am, and that therefore my remarks would merely serve as a kind of pivot on which to hang the opinions and thoughts of persons who are really well acquainted with it. I must confess, sir, as the time drew nearer I became a little nervous, and I thought it my duty to look up what has recently been written or said about the relationship of lymphadenoma to tuberculosis. And I discovered, to my great pleasure, an account of a discussion at Cheltenham, at the meeting of the Pathological Section of the British Medical Association, on this very subject, namely, the relation of lymphadenoma to tuberculosis. I read the discussion with avidity, because I wished to become acquainted with the opinions which were expressed, and even hoped to make use of them, if possible, at this meeting. But when I had read the discussion I would have none of it, because it was apparent to even a very superficial observation that, unless by chance, no two persons were talking of the same disease. Professor Michell Clarke introduced the discussion, and defined, in a

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loose kind of way, what he meant, or what is generally meant, by lymphadenoma; and he proceeded to discuss the characters of the disease, and afterwards to compare a disease so loosely defined as this with other diseases still more loosely defined, such as lympho-sarcoma and leukæmia, and then to compare it with perfectly well-defined diseases, about which nobody has any doubt,—such, for instance, as tubercle. No wonder the discussion was barren in results; and it struck me, sir, that if our discussion to-night is to have any value in the present or in the future, it can only be after we have thoroughly defined what we mean by lymphadenoma. I know of no disease for the last twenty-five or thirty years which has been treated in so singular and curious a fashion as has lymphadenoma. If, for instance, I show such cases as these two little boys[1] in the consulting room at St. Bartholomew's Hospital, one of my colleagues says, "Yes, I think that is lymphoma;" another says, "I think it is lympho-sarcoma;" a third says, "I think that is lymphadenoma," and I do not know that they do not all mean the same thing. On the other hand, I do not know that they are not speaking of different diseases. There are also other terms applied, such as leukæmia, lymphatic leukæmia, splenic leukæmia, and the like. And then a different classification seems to rest upon how many corpuscles the blood contains, or whether it contains one particular kind of corpuscle. So the definition of this disease is one of the most unsatisfactory that I know of in connection with such a serious and important disease as lymphadenoma.

In the first place, let me say that when I am speaking—for I can only give my own definition—of lymphadenoma I have in my mind a case such as is presented by one of those two boys; I have in my mind a patient with an enlarged gland, or group of glands, or groups of glands; glands which perhaps are soft, just as they are in those two boys, and not firmly matted together, but not separable from each other. And after a time—the disease sometimes lasting for several years—these glands may become adherent to the surrounding parts, so that if one came to take them out it would be very difficult, and indeed impossible, without removing a good deal of the

[1] Two boys suffering from lymphadenoma were shown to the Society by Mr. Butlin.

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surrounding textures. Then I know that in the course of time the spleen and liver and other parts may become enlarged, although they do not invariably do so, and I know that glands in other parts of the body may become affected in a similar way, and I know that the blood, in some cases, undergoes more or less serious change. When I have that disease in mind, and talk of it, I call it the soft form, using the old nomenclature of lymphadenoma. And I have in my mind another form of lymphadenoma, in which the glands are exceedingly hard, feeling like very firm fibrous tissue, bound not merely to each other, but to the surrounding parts, and fixed so firmly that no surgeon would dream of attempting the removal of them. Then, sir, if I take those specimens on the table which we have brought here of parts which have been removed mostly after death, and I refer to them, I have in mind a special disease. It never occurs to me that I am dealing with hypertrophy or tuberculosis of the lymphatic glands, neither do I think of it as an inflammatory affection. I know that I am dealing with a quite different disease. If I cut out the glands of one of these patients and make sections of them, I expect them to be quite homogeneous. I may be able to take some of them out quite easily, and one of them may be as big as a goose's egg. The cut section of such a specimen may look like a section of brain, or, perhaps, like udder, and it may have little blotches and spots or lines of blood-vessels upon it. If I examine the enlarged glands of different parts of the body I find always the same kind of thing, and I find this tissue, whatever it is, infiltrated in the surrounding parts, and I may find the glands matted together by it; and if there are secondary growths of this disease in other parts of the body—I suppose we may call them secondary growths—they have much the same characters,—that is to say, they look like sections of cut brain or udder. But let me point out again that these morbid appearances are not in the least like what one finds in an inflamed gland or a tuberculous gland or an hypertrophied gland: it is something quite different; it is something which we are not accustomed to find in any simple gland disease.

When I come to deal with that disease, I ask what class it belongs to. One person says, "I think it is more like tubercle;" another says, "I think it is a hyperplasia." And if I take the

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definition given of it at Cheltenham—it is the common definition which is put into the text-books—it is this: Professor Michell Clarke, in his speech, says, "The meaning to be attributed to the term lymphadenoma is that it comprises those diseases which are characterised by overgrowth of lymphoid tissue, or which give rise to growths closely resembling in structure that of lymphatic glands." Now, sir, when we deal with lumps in the human body, we classify them according to different methods, and we have in our mind, first, hypertrophy. We say, this is a mere enlargement of a previously existing part, that is, a hypertrophic or hyperplasic condition. Or again we say, these are enlarged from inflammation. Again, we take other diseases of which we know more, and we say, these are enlargements which are due to infective disease, such as tubercle or syphilis. We are able to classify them according to their cause. But when we come to lymphadenoma, we have absolutely no classification of it,—that is to say, no definite classification to which we can refer as one which is accepted by pathologists and surgeons. It is evidently not a mere hypertrophy in the first place; and secondly, it is not inflammatory; and in the third place, so far as I am aware—and I do not pretend to be versed in all the latest experiments which have been made on the subject,—it has not been proved to be one of the infective diseases. I understand that no organism has been definitely associated with lymphadenoma, and that it has never been successfully inoculated like tubercle. I admit that one of these days, it may be before long, we may be able to classify lymphadenoma as one of the infective diseases; but, as far as my knowledge extends, we are not able to do it at the present moment. When we are at our wits' end, so to speak, to classify masses or new growths, whatever they may be, and we are not able to put them into one or other of these different categories, we say, well, we will classify them for the time being, at all events, according to their structure; and that classification serves us very well indeed; it serves us so well that if, for instance, I remove an epithelioma of the tongue and have sections of it cut, and I take those sections to any microscopist, he may not even be very skilled, but if I take them to any one who is accustomed to the use of the microscope, and I say, "These sections are cut from an ulcer of the tongue," he takes the slide

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and looks at it and says, "Yes, that is the typical structure of epithelioma." He knows what he means by that, and I know what he means. And if we talk in a place like this of epithelioma of the tongue, at once a certain general disease is before our minds and the special microscopic structure which belongs to that disease. And that is what I should like to do in the case of lymphadenoma. But directly I approach the subject I perceive a lack of definite knowledge. I sometimes ask at my Fellowship Classes at the hospital, and I also ask my dressers and other students, this question: "What is the structure of lymphadenoma?" and the answer is always the same, "It is an hypertrophy or an increase in the natural constituents of lymphatic glands." And that story has been, as far as I am aware, repeated over and over again, until really it is received as a kind of gospel truth, and nobody has dared for many years to definitely state that it is not true, and that there is a definite structure belonging to lymphadenoma just as there is a definite structure belonging to epithelioma, or as there is a definite structure of spindle-celled sarcoma. And I trust to-night that we may make a determined attempt, by introducing into our 'Transactions' descriptions and drawings of the specimens which are exhibited, to define what we mean, and what this Society understands, by lymphadenoma. I am sure it may be done, from the study which Dr. Andrewes has made with me on the subject, and from certain matters which came under my notice some years ago. If it would not be trespassing too much on your patience I would tell you what happened in a case of lymphadenoma, and how my attention was directed to the possibility of recognising lymphadenoma just as certainly by its structure as we do other new growths. It is an interesting story in its way. What happened was this:—Four or five years ago a young lady was brought to me from one of the large towns of Lancashire by a medical man. He said, "I wish to put to you two questions in connection with this case. This young lady is said to have tuberculous disease of the glands of the neck, and she is engaged to be married to a gentleman who lives in South Africa. The questions we ask you are whether any further operation shall be practised upon her —she has already been operated upon; and in the second place, whether her father's suggestion that she shall be married

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at once and go out to South Africa, as a country the climate of which is good for tubercular disease, should be followed out." I said, "Very well." But directly I examined the patient I could see that there was no doubt at all, nor could there be doubt in the mind of any reasonable person, that she was suffering not from tuberculosis, but from the hard form of lymphadenoma, as she had scars in the neck over a mass which was as hard as a piece of stone. As to performing any further operation on her, it was absolutely out of the question; and as to the second suggestion, I was obliged to say it is an outrageous thing, it is not to be considered for a moment. And then I asked how it had come about that she was supposed to be the subject of tuberculous glands. He said, "Portions of these masses were sent to the Clinical Research Association, and we have received the report with them; and here is the report." That report was signed by a former secretary to this Society. It was much longer and more elaborate than usual, and it was to this effect: that the examiner of the sections could not quite make up his mind as to the structure, but although it was not typical of tubercle, he thought it was as much or more like tubercle than anything else. Not being sure about it, he said that he had taken the liberty of submitting the sections to a surgeon in this town who is distinguished for his knowledge of pathology, and also for his knowledge of tuberculous diseases. The name of that surgeon has never been revealed to me to this day. But he said that the surgeon stated, "I cannot say that it is tuberculous, but all I can say is that if it is not tuberculous I do not know what it is; and upon this followed these curious results. Well, sir, I did not stop there. I said I should like to see the slides. I obtained a slide and I looked at it, and saw that the structure was a very unusual one. I was bound to admit it was a structure I was not familiar with, and, as I generally do under such circumstances, I went to our 'Pathological Transactions,' and turned instinctively to the twenty-ninth volume, which contains a report of the exhibition of lymphatic diseases, particularly lymphadenoma and Hodgkin's disease, in the winter of 1877–8. I thought I should like to see the pictures of lymphatic glands which were shown, and their microscopic structure, so that I might see whether this corresponded with any of them; and I found a very curious thing

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to begin with. There are very few pictures in any of our 'Transactions' of the microscopic structure of the glands in lymphadenoma; and even in that particular volume of the 'Transactions' there are scarcely any pictures of the microscopic structure of the glands in lymphadenoma; and although that discussion is illustrated by excellent pictures of people with lymphadenoma, pictures of the gross morbid appearances of lymphadenoma, as well as of the microscopic structure of the liver and spleen and kidneys and bones and skin and of all parts of the body in lymphadenoma, there are only four pictures of the microscopic structure of the glands in lymphadenoma. One of them is of Dr. Sutton's case, in which the glands were very little enlarged, and could not be considered to be characteristic. Another is of Dr. Dickinson's case on the relation of lymphadenoma to tubercle. The drawings are made particularly to show the tubercle, and not the structure of lymphadenoma. And then there is Dr. Ridge Jones's case of what might be called lymphatic leukæmia. The drawing of the gland was made by Dr. Whipham. And last, there is one picture by Dr. Greenfield of what may fairly be called a typical gland of lymphadenoma. Directly I compared my slide with that drawing I said that the drawing might very well have been taken from this slide; it showed precisely the same structure. It was not the structure of an enlarged gland, it was almost more like that of carcinoma. Then I determined to go a little further, and as Dr. Kanthack was still in the Pathological Department at St. Bartholomew's Hospital, I took the slide down to him, and I said, "Look here, Kanthack, here is a slide taken from an enlarged gland in the neck of a young woman. Will you look at it and say what you think?" He put it under the microscope, and just in the same time that he might have taken to examine an epithelioma or a spindle-celled sarcoma he said, "Yes, that is the characteristic structure of lymphadenoma." And that was the first time I ever heard that it had a characteristic structure. At that time Kanthack was working at lymphadenoma. I do not know how far he would have gone with it, but I am sorry to say he left soon afterwards to go to Cambridge, and I seldom saw him and was not able to talk to him again on the subject. Then I wrote to the gentleman who made the report, and reproached him, as I think I had a right to do—for I was his President

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when he was a Secretary of this Society—for not having studied his 'Pathological Transactions.' He examined the drawings and agreed with me. I was very much impressed with the circumstances of this case, and I determined, if ever I got the chance to do so, that I would take up the study of lymphadenoma. Soon after Dr. Andrewes was appointed to our hospital I told him the whole story, and begged him to be so kind as to associate himself with me. I said I would collect cases, take them into the hospital, and try particularly the effect of arsenic upon them—of that I shall not speak to-night, I will bring it forward at some future time,—and I would take out a gland in every case for microscopic examination. We would keep our sections, and we would follow up the cases as far as possible and find out what organs were affected, and whether the same kind of structure as occurred in these two or three cases we knew of was to be found in every case of lymphadenoma. I am happy to say he was good enough to take up that part of the subject, and he will tell you that we can now as definitely recognise the structure of lymphadenoma as we can recognise the structure of many other diseases. We can recognise a typical structure which is not the structure of an ordinary enlarged gland, and we hope that wherever that structure is found in a new growth it will be recognised as the structure of what we now call lymphadenoma. What will become of lympho-sarcoma, lymphoma, and the rest I do not know.

With regard to the relations of this disease to tubercle, I can state in three sentences all that I know about it. In the first place, the disease I have been talking about is certainly not tubercle. In the second place, the disease I have been talking about does not in the least exclude tubercle, nor does it seem to render a patient in the least degree immune to an attack of tubercle. And I would go a step further, and say I have a suspicion that lymphadenoma renders a patient, on the whole, a little more disposed or liable to an attack of tubercle than he would be if he were not suffering from this particular disease.

THE PRESIDENT.

The subject of lymphadenoma is an extremely important one, and it is very difficult to define what is meant by the term.

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In discussing the relation between lymphadenoma and tubercle, I presume the point at issue is whether, as has been asserted by some, the cases diagnosed clinically as lymphadenoma are not really examples of acute glandular tuberculosis, or whether there is a disease, lymphadenoma, distinct from tubercle on the one hand, and from lympho-sarcoma, etc., on the other; and, further, whether this disease produces histological changes in the glands which are peculiar to and suffice to distinguish it. Clinically it is certainly often a matter of extreme difficulty to be sure as to the true disease of a mass of enlarged lymphatic glands.

F. W. ANDREWES.

I am anxious to confine my remarks as far as possible to the strict subject of this evening's discussion—the relation between lymphadenoma and tubercle. The subject may be approached from at least three sides: the clinical, the histological, and the bacteriological and experimental. Mr. Butlin has dealt so fully with the clinical side of the question that I have little to add to the views which he has advocated, and with which I am in complete accord. I therefore propose to confine myself to the histological and bacteriological aspects of the subject, and I shall speak, as far as I can, from the results of my own personal observation and experience. During the past three years I have devoted a considerable amount of time to the investigation of cases of lymphadenoma, from material supplied to me, to a large extent, by Mr. Butlin himself, as part of a prearranged system of investigation, to which I have added such other cases as the chance of the *post-mortem* table and the operating theatre have afforded. During these three years I have investigated some twenty cases, many of them in considerable detail.

Every one who attempts to discuss the subject must define for himself what he means by lymphadenoma. It is unfortunate that so many different terms have been used for it. To an English audience it is perhaps enough to say that I mean "Hodgkin's disease." It is the condition to which Virchow, who fully appreciated its histological characters, applied the term "lympho-sarcoma," a term now used by most writers in a different sense, and which, in my humble

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opinion, might well be discarded. It is the condition described by Billroth as "lymphoma malignum." The peculiarly unfortunate term "*pseudo*-leukæmia" has been used for it by Cohnheim and others. I mean by it a disease characterised by a progressive enlargement of the lymphatic glands and of the lymphoid tissue of certain internal organs, notably the spleen and liver, unattended by the indiscriminate metastasis of sarcoma, and characterised by what I believe to be a definite histological change in the lymphatic tissues affected. The condition differs from ordinary sarcoma in its especial predilection for lymphatic tissues, in the absence of true infiltration of adjacent structures, and of metastasis in its ordinary sense. The blood changes are not distinctive.

Now in typical cases of the disease, conforming to the above definition, there is found in the affected glands a set of histological changes of a fairly constant description, and which I have endeavoured to illustrate in the microscopic specimens shown this evening. In a normal lymphatic gland there exists a fibrillar reticulum upon which are set large endothelial cells; this forms the framework of the gland, and its interstices are filled with innumerable lymphocytes, more or less obscuring the framework. In sections of normal glands which have been stained with eosin and methylene blue, I have always found it possible to demonstrate cells with eosinophile granulations. These are scanty and chiefly present about the lymph sinuses at the periphery of the gland. I do not know their significance; they are very unlike the eosinophile leucocytes of the blood. Further, the tissues of a normal gland habitually show a follicular arrangement in the cortex, in which more transparent "germinal centres" are to be recognised, while in the medulla the adenoid tissue forms a plexus of branching and anastomosing trabeculæ. The distinctness of this arrangement varies in different glands; for example, it is far more conspicuous in a cervical than in a mesenteric gland. Now, in true lymphadenoma I have found, as everyone else has found, the following changes:— (1) The general plan of the structure of the gland is obscured and simplified; the distinction between cortex and medulla is abolished, or nearly so, so that the whole gland has a more homogeneous appearance. (2) The number of lymphocytes is apparently very much decreased; they are proportionately

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scanty, and no longer conceal the supporting framework of the gland. (3) In correspondence with this, the framework has undergone hyperplasia, the fibrillar reticulum is conspicuous,—its increase may amount to an actual fibrosis. The endothelial cells in connection with it are more numerous and much more evident; here and there some of them attain a very large size, and may contain two, four, or more large and deeply stained nuclei. These are the cells especially characteristic of lymphadenoma, described by Virchow, and I think an endothelial origin may fairly be ascribed to them. They are especially numerous in the soft, rapidly growing forms of the disease; they are not always uniformly distributed, but sometimes occur numerously at special places, and I have been able to demonstrate large and beautiful karyokinetic figures in them. They may properly be called "lymphadenoma cells," and though they are large, multinucleate cells, they have little resemblance to the giant-cells met with in tubercle. They are not so large as the latter, they are more rounded, and their nuclei, fewer in number, are larger, stain more deeply, and occupy a more central position; their protoplasm has less tendency to degenerative changes. They most nearly resemble the large cells found here and there in many rapidly growing sarcomas. (4) The eosinophile cells present in normal glands are always demonstrable in lymphadenoma, sometimes, but not always, in vastly increased numbers.

The essential histological features of lymphadenoma I take, then, to be a diffuse overgrowth of the glandular framework, with a corresponding apparent or real diminution in the contained lymphocytes. I lay stress on the diffuseness of the process; the whole gland is affected; one does not find islands of change in an otherwise unaltered gland, even in the smallest and least affected glands. Nevertheless the characteristic features may be better marked at one part than at another. There are varieties of lymphadenoma; a hard and a soft form are commonly spoken of, though intermediate grades exist. I have not met with evidence that the soft form ever passes into the hard, though this may perhaps occur. I think rather that the difference lies in the relative degree to which the elements of the stroma enter into the hyperplasia. Where the fibrillar reticulum is mainly affected a fibrotic, hard form arises, and in

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this the endothelial elements are not so markedly increased; the large "lymphadenoma cells" in particular tend to be scanty. In the soft, rapidly growing forms the endothelial hyperplasia is the essential feature; the "lymphadenoma cells" are numerous and large, while fibrosis is slight or absent. Finally, although the affected glands are singularly exempt from degenerative changes, such changes do occur. I have met with one case in which extensive hyaline degeneration was present. Further, foci of necrosis and caseation are sometimes seen. I am inclined to think they may perhaps be of tuberculous origin, at least in some cases.

It is unnecessary to go into detail with regard to the histology of tubercle, but it will not be out of place to emphasise one or two points in connection with tuberculosis of the lymphatic glands, and to insist on certain features in which the process contrasts strongly with lymphadenoma. Histologically, I recognise at least three forms in which tubercle attacks the glands. There is an acute miliary form, with or without caseation; there is a chronic caseating form, with or without fibrosis; and there is a much less common form characterised by great endothelial proliferation, with few giant-cells and little tendency to caseation.

In comparing the histology of tubercle with that of lymphadenoma, it is plain that in each case we are dealing with a process which has for its foundation an endothelial proliferation. The so-called "epithelioid" cells which form the mass of a young tubercle have, almost certainly in lymphoid tissue, and I believe always, an endothelial origin. Further, I should incline to class lymphadenoma with the infective granulomata rather than with autonomous new growths, though we are as yet ignorant of its exciting cause. But with these general facts the resemblance almost ceases. Tuberculosis in lymph-glands is at first a focal lesion. By fusion of different foci the whole gland may ultimately be affected, but one does not see a primitively diffuse affection of the gland as in lymphadenoma. The endothelial hyperplasia and the fibrosis are localised in tubercle, diffused in lymphadenoma, and the fibrosis in particular tends in tubercle to form a capsule, as it were, to the diseased areas; it does not uniformly permeate the gland. In nearly every case of tubercle the characteristic giant-cells are to be found.

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EXPLANATION OF PLATE IX,

Illustrating the communication by Mr. H. T. Butlin and Dr. F. W. Andrewes on Lymphadenoma in its Relation to Tuberculosis. (Page 297.)

FIG. 1.—Section of an axillary lymphatic gland removed from a man aged thirty-eight, affected with lymphadenoma. The disease was of six months' duration and rapid growth, appearing first in the axillary glands, and spreading thence to the groin and neck. The section, which is stained with hæmalum and eosin, shows the appearances characteristic of the soft form of lymphadenoma. The lymphocytes are much diminished in number, and there is a hyperplasia of the stroma. The large endothelial cells are conspicuous, and one of them shows a large deeply stained nucleus; the latter cell is of the kind typical of lymphadenoma. × 300.

FIG. 2.—Section of a cervical lymphatic gland removed from a man aged twenty-six, affected with lymphadenoma. The duration of the disease was one year, and it had spread from the neck to the axillæ. The section is stained with hæmalum and eosin, and differs from that shown in fig. 1 in the large numbers and great size of the "lymphadenoma cells." These are for the most part multinucleate and deeply stained, but do not resemble the giant-cells of tubercle. It is exceptional to find them so well marked as in this case. × 300.

FIG. 3.—Section of a cervical gland removed from a woman aged thirty-two. The disease was of eighteen months' duration. The glands were very hard, and formed a large mass in the neck; the inguinal glands were also enlarged. The section, which is stained with hæmalum followed by acid fuchsin and picric acid, illustrates the fibrotic or "hard" form of lymphadenoma. The gland is intersected by bands of dense fibrous tissue. This was the case even in the smallest glands removed. The details of structure of the lymphoid tissue can scarcely be seen under the low magnification; it was less affected than in the preceding figures, but the lymphocytes are somewhat decreased, and a few "lymphadenoma cells" are present. × 50.

FIG. 4.—Section of a lymphatic gland from the axilla of a boy aged eleven years, suffering from lymphadenoma of one year's duration. The disease, which was of the soft form, affected the cervical and axillary glands. The section is stained with eosin and methylene blue. It shows relatively decreased lymphocytes, and a conspicuous stroma with large endothelial cells. Numerous cells are present, loaded with eosinophile granulations. They do not appear to be related either to the endothelial cells or to the lymphocytes. It is unusual to find them in such abundance or so uniformly distributed throughout the glands as was here the case. × 650.

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Fig. 1.

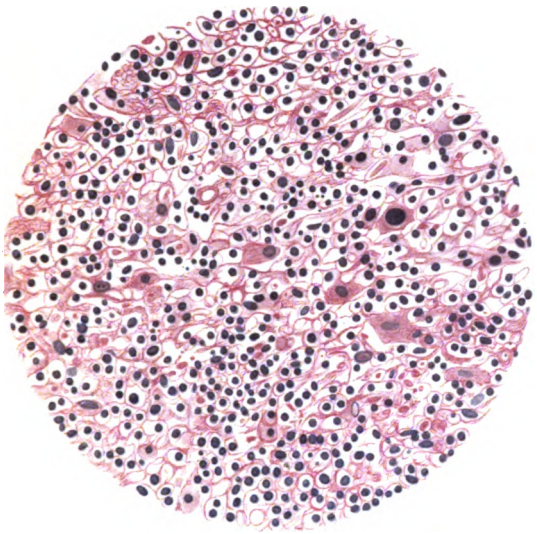


Fig. 2.

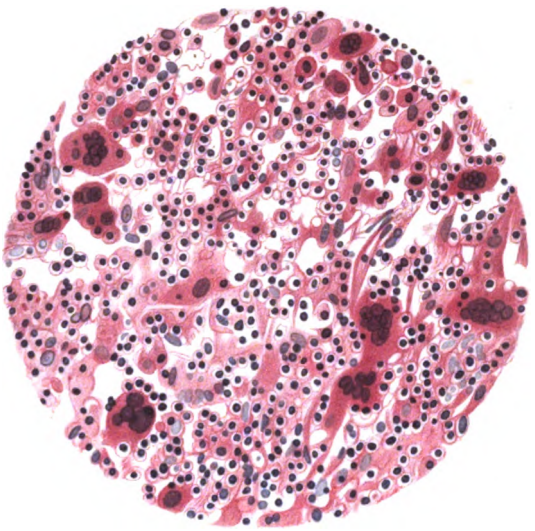


Fig. 3.

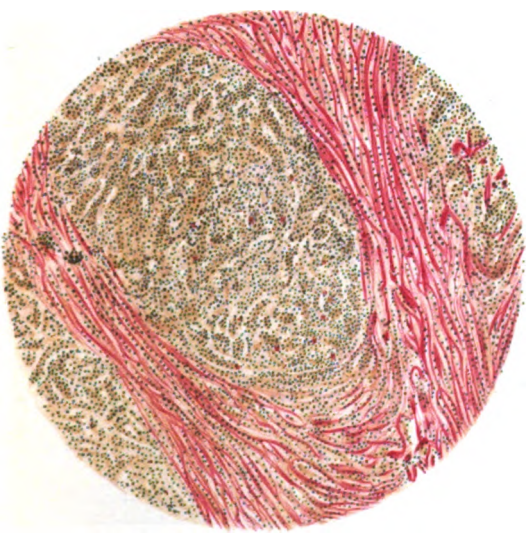
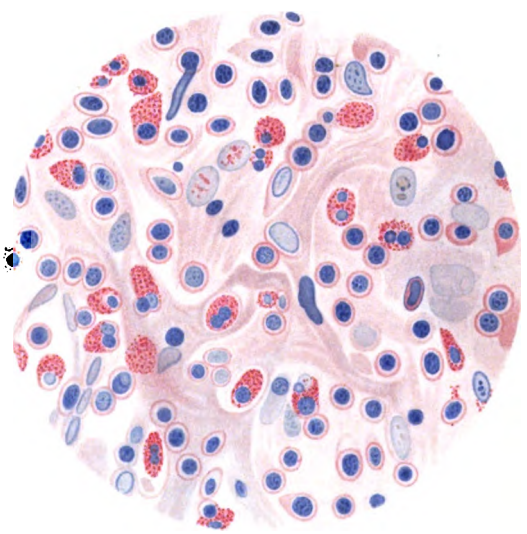


Fig. 4.



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I have mentioned the distinction between these and the typical lymphadenoma cells. It is said that such true giant-cells may occur in lymphadenoma. I cannot corroborate this; I should rather incline to the view that such cases were examples of a mixed infection. I cannot venture to say whether or not true lymphadenoma cells ever occur in tuberculosis of lymph-glands; again I should incline to regard such cases as of mixed nature, though with much diffidence. The eosinophile cells of normal glands are commonly much reduced or absent in tuberculous glands; Goldmann's original suggestion that this might furnish a diagnostic criterion between the two conditions cannot, from my investigations, as from those of others, be maintained, but it is broadly true that they tend to be increased in lymphadenoma, and diminished in tubercle. Finally, we have in the presence of tubercle bacilli very certain evidence that a given gland is tuberculous. It is often a matter of serious toil to find them in the glands, but it can generally be done in those cases which present the histological characters of tubercle. I have never succeeded in finding them in those glands which presented the pure and unmixed histological characters of classical lymphadenoma.

For the above reasons I am disposed to maintain that tuberculosis of lymphatic glands in its pure form is microscopically distinguishable from the pure form of lymphadenoma. I must further admit that cases are not infrequent in which the two sets of histological lesions are almost inextricably interwoven. I believe these to be cases of mixed infection, and I believe these cases to be the source of much of the confusion which has arisen on the subject—a confusion which has become perhaps worse confounded by indiscriminate animal experiment.

The discovery of indisputable tubercle bacilli—the production of tuberculosis in a guinea-pig by inoculation of portions of a gland with due aseptic precautions—these are positive evidences which naturally cannot be gainsaid. They prove that a given gland is tuberculous, but they do not disprove the possibility of its being also lymphadenomatous. Herein, I think, lies the fallacy into which those have fallen who have relied on animal experiment as establishing the identity of the two conditions. Their argument is this: "Here is a gland which, on microscopic and clinical evidence, you pronounce lymphadenomatous. I

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inoculate it into a guinea-pig, and behold! the animal develops tubercle. Therefore lymphadenoma is tubercle." I have often wondered how many guinea-pigs inoculated with a series of bronchial or mesenteric glands from chance indifferent cases in the *post-mortem* room would develop tubercle.[1] I take it that our lymphatic glands are bacterial filters, which, in every one of us, must retain many an inhaled or ingested tubercle bacillus, doomed to destruction where the soil is unsuitable for its growth. What wonder that a certain proportion of such glands give rise to tubercle when inoculated into the susceptible soil provided by the guinea-pig? Gland tuberculosis is an extremely common affection; lymphadenoma is a much less common one. I know of no evidence pointing to any antagonism between the two conditions; on the contrary, I should rather be prepared to believe that lymphadenomatous glands were a favourable soil for the growth of the tubercle bacillus. The glands of a case of "Hodgkin's disease" must be as exposed to the invasion of chance bacilli as normal glands, while, probably, they are less resistent. The mathematical chances of the co-existence of the two conditions in certain cases, though naturally small, are not negligible.

I do not know whether anyone here present this evening is prepared to maintain the tuberculous nature of all cases of lymphadenoma which are not leukæmic or sarcomatous. It is possible that there is, for at the recent discussion on the disease at the Cheltenham meeting of the British Medical Association, more than one speaker expressed great scepticism as to the existence of a true lymphadenoma apart from these conditions.

I am able to show specimens this evening from at least one case which is strongly opposed to such a conclusion. The case is a strong one, because it happens to be an example of acute lymphadenoma in a boy of seven, running its whole course up to a fatal termination in some four months and a half. It was in all respects a typical case of the acute form of the disease, and the *post-mortem* appearances were characteristic of lymphadenoma without any suggestion of tubercle. I show prepara-

[1] As a matter of fact such an experiment is recorded by Pizzini ('Zeitschrift f. klin. Med.,' 1892, xxi, p. 329). He inoculated guinea-pigs with glands from forty bodies, dead of non-tuberculous affections, and found tubercle to result in 42 per cent. of the cases. The bronchial glands were the ones that most frequently yielded a positive result.

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tions of the lymphatic glands at the root of the lung and of the spleen, together with microscopic slides of the lymphatic glands and pleura. In none of them is there the slightest appearance of tubercle, and a portion of one of the glands, inoculated subcutaneously into a guinea-pig, produced no tuberculosis. Now if lymphadenoma were but a variety of obscure gland tuberculosis it is almost incredible that this fairly complete examination should not have revealed the fact; and the acuteness of the case seems to me to forbid the supposition of obsolescence or death of the tubercle bacilli. Indeed, this one case is sufficient to convince me that there is a true lymphadenoma which is non-tuberculous.

If the disease were truly due to the tubercle bacillus, there should be at least some approach to uniformity in the effects of animal inoculation. I have not found this to be the case. The number of instances in which I have performed animal inoculations is unfortunately small—only some four or five altogether,—but in addition to the above negative result I can record two others in which the conclusion is opposed to the tuberculous nature of lymphadenoma. In one the patient died with a diffuse affection of nearly all the lymphatic glands in the body. The glands were moderately large and curiously translucent, owing to extensive hyaline degeneration of the stroma (as is seen in a section shown under the microscope). One of the bronchial glands was, however, caseous, and this gland, inoculated into a guinea-pig, produced a tuberculous abscess in which tubercle bacilli were readily demonstrated. A portion of another and much larger gland, from the neighbourhood of the pancreas, in which no caseation was visible, was inoculated into another guinea-pig at the same time. This animal died soon after the other, and though it presented a small local abscess, no tubercle bacilli could be found either here or elsewhere, even after prolonged and careful search. In a second case, in which the cervical, bronchial, and axillary glands presented the appearance of lymphadenoma, and in which the microscopic characters of the glands were typical of that disease, I inoculated part of one of the axillary glands into a guinea-pig without any result. Yet in one of the cervical glands from the neighbourhood of the larynx, a section prepared by Dr. W. Jobson Horne, and shown to-night under the microscope, exhibits a typical tubercle with a

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giant-cell and three tubercle bacilli, although the bulk of the gland shows the structure of lymphadenoma. Such cases as these may possibly be open to some criticism, but in my opinion the reasonable interpretation of them is that they are cases of true non-tuberculous lymphadenoma, upon which a localised tuberculous infection had been accidentally engrafted.

I bring forward this experimental evidence, scanty as it is, as proof that there is a lymphadenoma, with the characteristic microscopic features of the disease, which does not depend upon the presence of tubercle bacilli. I am most ready to acknowledge that there is a progressive glandular affection, truly tuberculous in nature, which clinically, and even on the *post-mortem* table, may closely simulate lymphadenoma, and which has been confused with it. Examples of this are recorded in the literature of the subject; and although I have not so far met with any case of a purely tuberculous progressive lymphadenitis which could not be recognised as tuberculous on the *post-mortem* table, I have seen cases which approach this very closely. I will mention briefly one such case, although I am not sure that it had not a lymphadenomatous basis. The patient was a man of thirty-five, admitted to hospital with severe purpura and hæmorrhages from the nose, mouth, and kidneys. He had recurrent febrile attacks, and the spleen was evidently enlarged. After he had been more than two months in the hospital the cervical and axillary glands became enlarged. The blood-count showed only 3000 leucocytes per c.mm. The case was diagnosed as lymphadenoma, and when the patient died of peritonitis, after being under observation for more than five months, the autopsy appeared to confirm the diagnosis. The cervical, axillary, and mediastinal glands were much enlarged, pale, firm, and not caseous; they presented to the naked eye no evidence of tubercle. The abdominal lymph-glands were in a similar condition, though here the enlargement was less. The spleen weighed 28 oz., and was densely studded with white nodules, exactly like those seen in lymphadenoma. The lungs were free from tubercle, and the peritonitis was not apparently tuberculous. In fact, although the question was fully discussed in the *post-mortem* room, the most careful search failed to reveal any sign whatever of old or recent tuberculosis. I think no one had any doubt that the case was one of lymph-adenoma, and, indeed, a typical case. I inoculated a guinea-pig

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with a portion of an enlarged tracheal gland, and in a few weeks the animal began to show evidence of tubercle, of which it ultimately died. Sections of the affected glands from the mediastinum and mesentery of the patient showed marked fibrosis, and contained unequivocal tubercles. I found tubercles in the spleen, and the liver was thickly set with minute growths which had escaped naked-eye observation, and which were not typical of tubercle histologically, though I succeeded in demonstrating tubercle bacilli in them. I also found bacilli in one of the mediastinal glands. The man had therefore died not merely with a localised tuberculous infection of a chance tracheal gland, but with generalised tuberculosis, which had entirely escaped detection during life and on the *post-mortem* table. To decide whether this was engrafted on a lymphadenomatous basis is very difficult. Although tubercles were found in the lymphatic glands and spleen, these were isolated and infrequent; the general histological impression left by a study of the sections was rather one of lymphadenoma, though not of the typical form. The appearance of the spleen was strongly in favour of lymphadenoma. The case illustrates the extreme difficulty of deciding the question, even after full examination, and I do not feel able to pronounce a decided opinion. But I do strongly feel that such cases should not necessarily be regarded as settled because one obtains evidence of tubercle.

Did time permit, I could recount to the Society the details of other most puzzling cases in which the lesions of tubercle and lymphadenoma appeared simultaneously present. I have, in particular, very full notes on two cases of Mr. Butlin's, in each of which I examined excised glands a year or more before death, and later had opportunity for complete investigation. One was a case of apparent lymphadenoma, in which the patient died of acute general tuberculosis, with his lymphadenomatous glands seemingly cured by arsenic. The other was a boy whose original excised glands showed evidence both of tubercle and lymphadenoma, and who died with an enormous liver containing masses of new growth presenting mixed characters of the two conditions. But I feel that the adequate discussion of such difficult cases would need the bringing forward of too great a mass of detail; they need separate publication.

I will conclude by formulating the conclusions to which my

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own observations on the relation between tubercle and lymphadenoma have led me.

1. Lymphadenoma is a distinct and separable disease, not due to the action of the tubercle bacillus. I believe that in its pure form it is histologically recognisable.

2. There is a form of tuberculosis of the lymphatic glands clinically indistinguishable from lymphadenoma, but recognisable by histological and bacteriological examination.

3. There occur a fair number of cases of lymphadenoma in which secondary infection with tubercle has taken place. Often this secondary infection is local and unimportant; at other times the tuberculous element gains the upper hand, and the patient may die of generalised tuberculosis, and with a mixture of lesions of the most puzzling kind. It is from cases of this description that confusion has naturally arisen, whence the belief, in certain quarters, that lymphadenoma may be merely a special manifestation of tubercle.

Although I bring forward these opinions in somewhat dogmatic fashion, I do so, in reality, with much diffidence, because I believe that there are few important pathological problems so difficult or so beset with fallacy. I have been glad to find, from a perusal of recent literature, both here and abroad, that there are many others who have been led to the same point of view. I do not claim to be able in every case to tell lymphadenoma from tubercle under the microscope. The most that can be said is that, given a pure case of lymphadenoma and of tuberculosis respectively, it is possible to discriminate between them with tolerable ease.

L. Dickinson.

My contribution is a very modest one, and I had hoped to hear the views of more authorities and the contributions of more members generally before I made my remarks. The reason why I have been honoured with an invitation to speak is that lately I have had under my care a patient with well-marked lymphadenoma, generalised, in which case the question of tuberculosis was raised by some of those who saw the patient at the Clinical Society last April. It was to be hoped that now that the patient is dead, and has been examined more fully than was possible

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before, the case might prove to be of some value in connection with this question of the possible relationship of tuberculosis and lymphadenoma; but I am not sure that the Society will think so. I feel, rather, that the case will be regarded as an equivocal one, and perhaps incomplete, which, however, does not matter so very much, because what Mr. Butlin has said and what Dr. Andrewes has said, has to a large extent settled the question that tubercle and lymphadenoma are not intimately associated. The presence of tubercle in the body was established, but it certainly was not proved, to say the least of it, that the whole disease was tuberculous. In brief outline, the case was that of a boy aged 16, who died last August, after having suffered for more than two years from enlargement of the lymphatic glands, at first in the neck, but eventually general, without the least tendency to caseation, suppuration, or any of the recognised signs of tubercle. Clinically, the case was out of the common, because of an extensive deposit of lymphoid growths in and beneath the skin, many of which subsequently disappeared, while others became involuted to a remarkable degree. The cause of death was inanition and exhaustion from pressure by the abdominal glands, contributed to by a high degree of anæmia, but without disproportionate lymphocytosis. *Post mortem*, the main facts were that the pelvic and abdominal glands were greatly enlarged, and firm and pale on section, but nowhere was there any sign of degeneration. The great vessels of the abdomen were surrounded, if not compressed, by the glands. In the thorax was a large bunch of glands at the base of the heart. The liver was large and pale, but not otherwise abnormal to the naked eye. The spleen weighed 1 lb. 9 oz., and contained many masses of growth, which were not quite like those of ordinary lymphadenoma, inasmuch as they were reddish in colour, rather than white or yellow. The lungs were free from any morbid appearance, but a small mass of growth came from the periosteum of one of the ribs. In the cranial cavity were three small masses of growth, depending from the inner surface of the dura mater. The bones in general were not examined, but on account of certain clinical indications the left tibia was divided vertically, and the upper part of it displayed two or three yellowish-white patches in the medullary cavity. That specimen is on the table. Bacteriological cultiva-

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tions were made by Dr. Charles Slater from the abdominal glands and from the spleen, and resulted in a copious growth of streptococci—a point of no great importance, or, at any rate, of no novelty. All the diseased parts were examined microscopically, and, with the exception of the liver, they all showed the same kind of change, which it is superfluous that I should describe now that we have heard from Dr. Andrewes what it generally is in true lymphadenoma, for the sections are at the disposal of any one who cares to examine them. The notes I have here are merely to the effect that there was a highly cellular lymphoid structure, with a fibrous reticulum of varying density, and that in the spleen, which was highly fibrotic on the whole, the coarser trabeculæ enclosed areas of small round-cells with but an obscure reticulum; but there were no giant-cells, and no caseation anywhere. Many of the lymphatic glands and the spleen were carefully stained and examined for tubercle bacilli, but with an entirely negative result. When the liver came to microscopical examination it unexpectedly proved to be decidedly lardaceous, both anatomically and in its reaction to methyl aniline violet. But the important point about the liver is, that one of the sections disclosed a small nodule of undoubted tubercle; that is to say, there were giant-cells, and there was an area of central caseation, and the presence of a few indisputable tubercle bacilli was determined. This little area in the liver is quite evident to the naked eye on the slide which I have here, but in the *post-mortem* room it was probably just on the limit of naked-eye vision; at any rate, it escaped detection at the time, and there may have been several others in the liver, though certainly there were no others in the many small portions which were preserved for the microscope. Nevertheless, here was positive evidence of the existence of tubercle in this patient. The lardaceous state of the liver I do not think has any important bearing upon the case one way or the other as regards tubercle or lymphadenoma. But it is worth remarking, because some years ago there existed an idea that lardaceous disease and lymphadenoma were pathologically associated; and when Sir Samuel Wilks (then Dr. Wilks) opened a discussion upon lymphadenoma before this Society, which is reported in the twenty-ninth volume, to which Mr. Butlin has already drawn attention, he suggested

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the question of that relationship as one of the points for discussion. But although lardaceous disease was far more common then than now, and although the contributors to the debate were very numerous, yet no one even so much as touched upon this question, and I think that that may be taken as sufficient proof that there is no essential relationship between the two conditions. The two great causes of lardaceous diseases are, of course, suppuration and syphilis; but a third occasional cause seems to be almost admitted, namely, profound cachexia of different origin—from malaria, for example. This particular patient was not malarial, nor did he suffer from suppuration or from syphilis, but for some months before his death he had been in an advancing state of enfeeblement and anæmia, ending in profound cachexia, which is the probable explanation of the lardaceous liver.

Now, to return to the glands, of course it is to be regretted that the final test of tuberculosis, viz. inoculation experiments upon guinea-pigs with the fresh pulp, was not employed. The fact is that at the time we were not so fully alive as we should have been to the importance of employing this test in addition to the microscope; moreover, the *post-mortem* took place in August, which is rather a dead season for experimental work. But, looking at the whole case, at its clinical course, especially the remarkable involution which many of the growths in the skin underwent (quite unlike tuberculosis), and the remarkable fluctuations in the size of the glands, which those will remember who had an opportunity of watching the patient from week to week, and looking also at the *post-mortem* appearances, and the failure of the microscope to find anything like tubercle or tubercle bacilli in the tissues anywhere except in the liver, it seems reasonable to conclude that the essential disease was lymphadenoma. I express that opinion now with the less hesitation in consequence of what we have heard to-night. We may suppose that the limited degree of tuberculosis in the liver was simply a secondary infection. Our own 'Transactions' and the speech of Professor Michell Clarke, and the many references which he gave at the meeting of the British Medical Association in the summer, afford abundant evidence that lymphadenoma may supervene upon tubercle, and that tubercle may supervene upon lymphadenoma. I understood Mr. Butlin that lymphade-

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noma to some extent predisposes to an infection by tubercle. With that I should most heartily agree. It has been stated—I do not know whether with sufficient authority, but I gather from Dr. Andrewes that it was probably insufficient authority—that the microscope may not necessarily reveal the tubercle, and that inoculation experiments upon guinea-pigs are absolutely necessary for a decision. It is not for me to decide this question, and I have simply brought forward my case for what it is worth.

The drawing which I have brought and placed on the table is one of a large spleen weighing nearly 4 lbs. with a typical "hardbake" appearance, which was thought by everybody who saw it in the fresh state to be a spleen of lymphadenoma, but which proved when examined microscopically by Professor Delépine to be undoubtedly tuberculous. This spleen came from a woman of twenty-four who died in St. George's Hospital in 1887. She had suffered from enlarged glands much longer than from the enlarged spleen, and *post mortem* the glands in the neck, in the mediastinum, the axillæ, the abdomen, and the groins were all more or less enlarged and hard, and apparently quite free from tubercle. Recent tubercle was found in the liver and lungs. I bring forward the drawing as illustrating another probable example of tubercle supervening upon lymphadenoma which had already become fully established.

J. McFadyean.

I think Mr. Butlin, with remarkable modesty, said that one of his qualifications for introducing the subject which we are discussing to-night was that he probably knew less about the pathology of lymphadenoma than anybody else in the Society. I am sure that in that he was wrong, for I know far less about lymphadenoma than does Mr. Butlin—possibly less than almost any other member,—and therefore I am somewhat ashamed to find myself standing here at all. If the discussion had been confined entirely to lymphadenoma, and if that name had not been coupled with that of tuberculosis, I should most certainly have declined to say anything on the subject. When I came into the room I think my conception of what constituted lymphadenoma was probably the one shared by most of those who are present,—that is to say, it was founded upon the definition which one finds in

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the text-books. I supposed one should not call a case lymphadenoma unless there is present an enlargement of a considerable number of the body lymphatic glands, perhaps a general enlargement of these glands, and that enlargement is not associated with any great structural alteration in the gland, or with some degeneration such as caseation, or with leucocythæmia. We can now go away with different, and, I am sure, with more definite and more accurate notions as to what we ought to call lymphadenoma, since we have had the opportunity of examining Dr. Andrewes' beautiful series of sections and listening to his admirable paper. I have already said I am absolutely ignorant of lymphadenoma. I have never had the good luck to obtain for *post-mortem* or microscopic examination any case with disease of the lymphatic glands that appeared to me to be entitled to the term lymphadenoma. I can only recollect one case which I saw alive amongst the out-patients at the Royal Veterinary College. It was that of a horse that had bilateral enlargement of various groups of lymphatic glands in the body. That is a condition which is distinctly rare, and, unfortunately, I never saw the horse afterwards. In veterinary literature one finds it stated that lymphadenoma occurs in the lower animals, but one cannot read even the recent literature on the subject without a suspicion that the cases referred to may have been tuberculous. In fact, it is often too obvious that the diagnosis has been made on anatomical grounds only, and I therefore think there is even doubt as to whether any genuine case of lymphadenoma has been met with in the lower animals at all. Now that we have been taught that there is a disease of the lymphatic glands distinct from tubercle—and on that point I am satisfied—and having a special histology different from that of tubercle, it is possible that careful examination may show that this condition is also met with in the lower animals. Among the cases which until recently were termed lymphadenoma in veterinary literature, are those in which the spleen of the horse is the seat of enormous tumour-like growths. Another animal in which such growths are comparatively common is the pig. I have examined scores of such cases myself. Now, if one's diagnosis had to be based solely on the anatomical, coarse, macroscopic character of these lesions, it would perhaps be justifiable to call them lymphadenoma; but

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in the majority of cases there is absolutely no excuse for making any mistake with regard to the true nature of the lesions, or for failing to recognise that they are tuberculous. Nevertheless, the error was perfectly natural on the part of those who were quite ready to make a diagnosis on the macroscopic characters alone. In the great majority of these cases there is no excuse for making any error at all, because in many of them one can, without much trouble, demonstrate tubercle bacilli, and when one cannot readily demonstrate those bacilli one finds that the lesions have the same histology as those that one can prove to be tuberculous, either by demonstrating the bacilli or by inoculation. But I am in agreement with Dr. Andrewes that there are genuine cases of tuberculosis in which it is extremely difficult to demonstrate the tubercle bacilli. I would be almost disposed to go further, and say there are cases of genuine tuberculosis in which, unless one is prepared to spend a whole week in the examination of many hundreds of sections, it is not possible to demonstrate the bacilli. In the spleen of the horse, and occasionally in the spleens of the other domestic animals, there do occur tumour-like enlargements which are most positively not tuberculous, but which I can state with equal confidence do not possess the histology shown in Dr. Andrewes' specimens. These multiple, non-tuberculous, tumour-like growths in the spleen are almost entirely composed of cells of the lymphocyte type.

With regard to the question of the differential diagnosis of tuberculosis and lymphadenoma, it struck me that apart from the fact that in tuberculous lesions of the lymphatic glands one can, as a rule, obtain conclusive information as to their nature, either from an examination of their histology or from the demonstration of tubercle bacilli in them, or from inoculation experiments, there are other differences between lymphadenoma and glandular tuberculosis which ought to be of considerable assistance in diagnosis. It is not my experience that in any of the larger animals anything is met with that would deserve to be called a general lymphatic tuberculosis. I think that there is rather a wide-spread tendency to error in that connection. At any rate one sometimes reads an account of a case in which it was said that the lymphatic glands were universally involved. I can only say that in an experience of tuberculosis that is

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considerable, with regard to all the domestic animals that are naturally subject to it, and of cases in all stages, it has never yet been my lot to meet an animal in which anything like the whole of the lymphatic glands of the body were involved. But what appears to me to be a point of greater importance is this: that in tuberculosis the primary lymphatic lesions are, with remarkable constancy, found in certain groups of lymphatic glands, and I take it that these are not the groups of lymphatic glands usually involved in lymphadenoma; that is to say, they are the glands in near relationship to the throat, the upper cervical glands, the glands at the root of the lung, or the mesenteric glands. I suppose I am right in assuming that in a good many cases of lymphadenoma the glands at the lower part of the neck are involved while those higher up are healthy, or there is a lymphadenomatous condition of the axillary or inguinal glands without any associated visceral lesions. I am not prepared to say absolutely that there has never occurred such a thing as a primary tuberculosis of axillary or inguinal glands, but I very much doubt if such a thing ever did happen; at any rate, it must be highly exceptional.

NEWTON PITT.

The debate has taken a somewhat different line from that which I thought it would, and has rather resolved itself into the question of the identity of lymphadenoma as a special process, which can be histologically recognised in glands, rather than a discussion of the relationship, if any, that there is between tubercle and lymphadenoma. I confess that though I have at various times had the opportunity of examining many lymphatic glands, I cannot say I have ever been absolutely certain about some specimens. But I shall be very glad if, in the future, we can positively say, with regard to any section, that it is undoubtedly lymphadenomatous or that it is not. I would very much like the opinion of yourself, sir, and of others, as to whether such a definite statement can be made. It is possible to express a much more definite opinion about sections of liver and kidney, but there may be uncertainty about some of these sections in the earlier stages of the process.

What is the connection between lymphadenoma and tubercle?

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This depends upon what definition is given to the term lymphadenoma. At present we can give no satisfactory definite definition. There is, first of all, the clinical difficulty. We must all allow that there are cases which have been looked upon during life as absolutely typical of lymphadenoma, but yet in the *post-mortem* room we have found we were wrong. In looking through my experience of cases which have come into the *post-mortem* room during the past twenty years at Guy's Hospital, I find that out of 7000 cases there have been twenty which appeared to be due to lymphadenoma. Among these cases there were undoubted evidences of tubercle in four, although clinically they had appeared to be typically lymphadenomatous, and were not looked upon as tuberculous. I will refer to one or two points in connection with these.

One was that of a boy under the care of Dr. Wooldridge in the year 1888, who came in with enlarged glands in the groins, axillæ, and neck, and there was apparently no evidence of anything else abnormal. He only lived a short time, developing tuberculous meningitis, and the glands throughout the mediastinum and abdomen were also involved. There was also found a chronic fibroid tuberculous mass in the middle of one lung, with some chronic fibroid tuberculosis near it, and there were tuberculous ulcers in the intestine. There was no question whatever in this case that the boy had had tuberculosis, although clinically there was, within three days of his death, nothing whatever to suggest it.

A second case was that of a boy aged 4, with enlarged glands in the neck and along the trachea. He also died shortly after admission with tuberculous meningitis, showing caseous mesenteric glands, early tuberculosis in his liver and in his spleen, and there were one or two tubercles in the kidney.

The third case was that of a young man aged 26, who had enlarged glands. He had an enlarged spleen, severe diarrhœa, and ascites, and died from his diarrhœa shortly after admission. There were miliary tubercles in the lung, and the glands were caseous. There was no doubt that the mischief was, on the whole, tuberculous and not lymphadenomatous.

These are four cases in which the clinical evidence was in favour of lymphadenoma, and during life there was no suggestion of anything but lymphadenoma. In connection with such cases,

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I feel that it would be a great gain to our knowledge in future, if it were to become a general custom, for every lymphadenomatous patient to have an injection of tuberculin; until the question was cleared up, with the view of settling what proportion of these cases are tuberculous. My own opinion is that the connection is accidental, and not essential; but while it is still uncertain it would be desirable for all the typical cases of lymphadenoma to be treated with tuberculin, and provided the temperature was low and the dose only a milligramme, no risk would be run.

I have also notes of four other cases in which the appearances were typically those of lymphadenoma, both during life and *post mortem*, and yet in which, on hunting through the body carefully, there were found evidences of caseation. This raises the question whether caseation is a process which occurs in connection with lymphadenoma when there is neither tuberculosis nor syphilis present. I am extremely doubtful. The typical lymphadenomatous growths are very stable, the cells show very little tendency to degenerate or to become fibro-plastic; they remain without forming contracting masses, or showing caseating or hyaline degenerative changes. In the few cases where such changes have taken place, an associated tuberculous process is probably responsible. In one case the masses of glands, growths in the liver and spleen were typically those of lymphadenoma, yet in one gland there were two or three caseating centres. In another case also of lymphadenoma, typical both microscopically and to the naked eye, there were acute tuberculous nodules, which had caseated, scattered uniformly through the lung. There was not a single definitely caseous gland in the body. At the time of the *post-mortem* it was stated that it was thought these nodules in the lung were not tuberculous. Still, on considering the question I should be inclined to accept the view that if a number of small areas caseate very readily they are probably tuberculous. So out of twenty there were four which were undoubtedly tuberculous, four which had centres of caseation and showed the possibility of there being an associated tuberculous process, the remaining twelve showing no evidence of tuberculosis at all. Undoubtedly it may happen in some cases, although there are none of the characteristic appearances of tubercle, that the process may be due to a tuberculous infection;

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so we must consider the question whether lymphadenoma, if tuberculous at all, should be called a para-tuberculous process, like tabes dorsalis is regarded as a para-syphilitic process, and totally distinct in its character, its course, histological characteristics, and distribution, from any of the conditions with which one is familiar as due to tubercle. The extremely stable condition of the cells, their very slight tendency to vary, and the way in which they keep absolutely to the lymphatic tracts, seems to show that we have a distinct process from that of ordinary tuberculosis. Therefore I am not certain that, even if we accept the possibility of tubercle being one of the causes which can start lymphadenoma, inoculation experiments will necessarily settle the question. But against the possibility of lymphadenoma being a para-tuberculous process, I would refer to those cases of extremely acute lymphadenoma in which it seems very improbable there could have been time for the process to be tuberculous. A young boy had some enlarged tonsils, and was subject to epistaxis. His tonsils were removed, the epistaxis recurred, and he was admitted to the hospital. He died in nineteen days from the date he was first taken ill. On the eleventh day from the time the tonsils were enlarged there was enlargement of lymphatic glands and of the spleen and liver, and the histological appearances were those of lymphadenoma. It seems extremely improbable that if the process is a para-tuberculous one it could run such an excessively acute course, or, in this case, that the disease could have anything to do with tubercle. Take another case, that of a man who had gonorrhœa. Within a month he had an enlarged gland in his groin, within a few months general enlargement of the glands of the body, and he finally died with the typical appearances of lymphadenoma, without any trace of tubercle. Here, within a month of the starting of the local irritation, there was an enlargement of glands, and it is extremely unlikely that a process starting in that way in connection with gonorrhœa can be a tuberculous one. When we come to review a series of cases, the question may be raised whether we may not at the present time be including cases which differ histologically from the typical lymphadenomatous cases; and in future if we can settle the question by the characteristic appearances of the lymph-glands, then these must form a new group, and must no

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longer be called cases of Hodgkin's disease. At the present time we include under the term all those cases of patients who have enlargements of glands; the infection commencing locally and spreading to distant parts of the body, to which are often added enlargements of the liver and of the spleen, and finally a fatal termination. One case I may refer to is that of a man who had been a soldier, who gave a history of gonorrhœa, but no history of syphilis, and who, after a year's illness, died. At the *post-mortem* a large fibroid mass was found in his liver, a large mass in the mediastinum, and disseminated nodular lymphadenomatous masses were found scattered through the liver and spleen. He also had some paralysis of his third nerve. Now this seems to be a syphilitic process, with extensive changes in the liver, which has become infective, and has set up what appears to be an otherwise typical lymphadenomatous process. Yet the condition differs in some ways. On the one hand, all the material gave a lardaceous reaction; and on the other there was a very large amount of fibroid change. At the discussion which was held at Cheltenham it was insisted that there was a great tendency for lymphadenomatous masses to become fibroid. I should not be willing to accept this as the change which takes place in the liver, spleen, or kidney; it must be very exceptional indeed for extensive fibroid changes to occur in these organs in connection with lymphadenoma.

Another case in the series which followed on syphilis showed well-marked lardaceous reaction in the lymphadenomatous masses. There is no question, then, that some glandular masses which clinically appear to be lymphadenomatous do show lardaceous changes; but I hold that under the term lymphadenoma we at present include more than one process, and if in future we can definitely shut off one group, and say this is lymphadenomatous, and that others are infective processes following upon syphilis and other toxines, we shall have made a great advance in our knowledge of these conditions.

In all there are five cases which were probably syphilitic, and of which two gave a lardaceous reaction.

In two cases the process commenced in the intestinal mucous membrane as a lymphoid overgrowth, and these form a distinct group.

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A. *Four cases with definite evidence of tubercle at the* post-mortem.

1. John W—, aged 4, 1885. General enlargement of glands in neck, down the trachea, and up to the base of the skull.

. *Post-mortem.*—The glands are discrete, firm, sulphur-yellow, and all are more or less enlarged. Tuberculous meningitis and a considerable amount of tubercle in the lungs. Mesenteric glands caseous. Tubercles on peritoneum. Tonsils normal. Liver showed early tubercle, not caseating. Spleen, 12 oz.; firm, enlarged with numerous caseous tubercles about one eighth of an inch in size. One or two yellow tubercles in the kidneys.

2. Henry H—, aged 22, under Dr. Wooldridge in 1888. This was supposed to be a case of Hodgkin's disease, but he did not live long after admission.

Post-mortem.—Tuberculous meningitis. There were three large glands in the left anterior triangle, and a limpet-shaped mass of growth invaded the upper part of the right lung, projecting half an inch into the tissue. In the middle of the lung there is a chronic fibroid tuberculous mass, with pigmented fibroid tubercles near it. The tonsils were normal; there were tuberculous ulcers in the intestine. Liver, 62 oz.; tough, with nodules irregular to touch, yellowish in colour, many also small and ill-defined. Texture coarse and diffusely infiltrated in addition to nodules. The liver showed all the portal areas densely packed with small deeply stained cells, in size 5—8 μ. There was no caseation, nor did the cells show any tendency to organise and form fibroblasts. Some of the cells lay along the capillaries. The collections of cells were chiefly in the portal areas, but were spread over an area four to six times as great as the normal area, and they often surrounded a whole lobule as a thin layer. The collections of cells presented no definite evidence of tubercle. They differed from ordinary lymphadenomatous masses, and suggested inflammatory areas due to some acute infective process that had called forth a host of leucocytes, but they had neither accumulated in dense masses nor necrosed. There was no intra-cellular stroma, the cells were perivascular, and therefore presumably in the lymphatics. The collections of cells were sharply limited at their margins, and

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they were as densely packed at the margin as in the centre of a nodule. Flat masses of cells had also accumulated beneath the capsule of the liver, forming granulations on the surface. The glands near the pancreas were uniformly infiltrated with dense white growth. The pancreas was dense. Spleen, 16 oz.; consistency dense; appearance unusual. General overgrowth of fibrous tissue, with small ill-defined white nodules, but the main change was diffuse. Kidneys, 8 oz.; numerous ill-defined whitish firm nodules, one sixteenth to one third of an inch, scattered about, chiefly in cortex.

3. W—, aged 34, admitted in 1900, with a gland on the right side of his neck the size of a hen's egg. He developed pericarditis with effusion.

Post-mortem.—The cervical and mediastinal glands were enlarged, apparently due to Hodgkin's disease; one gland, however, was caseous. There was no tubercle in the lung. Sections of the glands showed a tuberculous process with giant-cells, fibrous tissue, and numerous round-cells. There were several centres of caseation.

4. Chas. T—, aged 26, under Dr. Pitt in 1890. Anæmia, œdema, pyrexia, normal number of leucocytes, a mass of glands in the left groin.

Under Dr. White in 1891. Ascites, with six pints of opalescent fluid. Slight leucocytosis. Death caused by diarrhœa.

Post-mortem.—Lungs universally infiltrated with grey miliary tubercles. No sign of old phthisis, no caseous foci. Enlarged glands along the trachea, one the size of a pigeon's egg at the bifurcation of the trachea, showing microscopically small round-cells, and in some glands there was central caseation. Thrombus in left subclavian vein. Glands in groins and axillæ enlarged. Great enlargement of mesenteric glands and of the glands along the aorta; one two inches across was caseous at one part and cystic at another; the rest of the glands were succulent and yellowish. The liver presented numerous little white nodules. The spleen weighed 46 oz. On section, numerous large white masses, others small and irregular in shape, and several large infarcts, some decolourised. The spleen looked like a blood sausage with lumps of fat in it. Kidneys, 11 oz.; decolourised

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infarcts, with lardaceous vessels. Microscopically the glands showed much fibrous tissue, with but few areas of normal lymphoid tissue. Parts were caseous and structureless, but no giant-cells were present. Lardaceous changes, with small aggregations of cells in the liver. Spleen, which was lardaceous and fibroid, contained giant-cells.

B. *Four cases in which there were caseating centres in the lymphoid growths.*

5. Chas. D—, aged 52, under Dr. Pye-Smith in 1883. Syphilis. The glands in the neck, axillæ and groins enlarged; large liver and spleen.

Post-mortem.—A large mass, 6 to 8 oz., of glands at the bifurcation of the trachea. Four pints of fluid in the pleura. Bronchial glands large and soft; mesenteric glands somewhat enlarged. Liver, 141 oz.; lower half of upper surface of liver and the left two thirds were infiltrated with a white mass of growth extending quarter of an inch deep. Otherwise no nodules, but a general infiltration, mottling it generally, but growing especially along the portal canals, where it often formed nodules one twentieth of an inch across. Behind the liver, in the portal fissure, was a mass of glands weighing 50 oz., many two inches in diameter, which had pushed the liver forwards. This mass surrounded the gall-duct and portal vein, but did not compress them. Two caseous masses in the pancreas, which was otherwise healthy. The masses of growth in the lumbar and mesenteric glands were soft, pinkish in colour, and did not yield a juice on scraping. That in liver was white and firmer. Spleen, 35 oz.; hard. One nodule, one inch across, irregular in shape, reached the surface; round the margin it was white, with an ochreous firm yellow centre; there were a few other superficial nodules, which were firm and white. Kidneys, 12 oz. Right testicle (body and epididymis) fibroid, with a few disseminated spots of caseation one twentieth of an inch across. Left testicle normal.

Probably the caseation was due to syphilis, and not to tubercle, of which there was no evidence.

6. Harry B—, aged 15, under Dr. Pye-Smith. General glandular enlargement. In November, 1890, short of breath;

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February, 1891, a swelling appeared in the left groin. Diarrhœa, vomiting, large tonsils.

Post-mortem.—Lungs free from tubercle, mediastinal glands enlarged, with a few caseous areas and hæmorrhages with dense fibrous tissue round them. Liver, 69 oz.; small-cell infiltration of Glisson's capsule. Glands enlarged and embedded in fibrous tissue. Spleen, 7 oz.; normal in appearance.

7. William D—, aged 16, under Dr. Goodhart in 1893. Enlarged glands in neck for two years; the mass has greatly increased in size in the past three months. Spleen enlarged. Diarrhœa. Pyrexia and emaciation. A hard mass of matted glands in the neck, measuring five and a half by three and a quarter by two inches, weighing 30 oz.; the largest gland was two inches long.

Post-mortem.—On section the glands are dry, tough and uniform, with the exception that there are numerous minute centres of early caseation, but no softening. The glands extend up under the maxilla and press upon the trachea, but do not extend into the anterior mediastinum. It is unusual to find in lymphadenoma even the small amount of caseation here noted. Lungs normal, small scarred tonsils. Liver, 48 oz.; a few small pale nodules less than one twentieth of an inch across, which, under the microscope, showed caseous centre and fibrous capsule. Minuter areas were not caseous, but looked like tubercles; none found elsewhere in the body. Spleen, 30 oz.; typical hardbake spleen. Nodules of lymphoid growth, none more than quarter of an inch across. A few showed early caseation.

The most striking feature in the microscopical sections of the *glands* is the great increase in the fibrous tissue diffused through the section, which is many times the normal amount. The bands running between the cells in the gland tissue are increased up to 20 to 120 μ in thickness. The number of cells is fewer than normal. There are scattered here and there a few very large cells which stain deeply.

8. Thomas M—, aged 12, under Dr. Pye-Smith in 1898. For two months he had enlarged glands, but no leucocytosis; he finally died comatose.

Post-mortem.—The lungs were normal. The glands in the

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groins and axillæ and along the bronchi were enlarged; one of the latter showed some coagulation necrosis. The other organs were normal in appearance.

c. *Two cases of lymphadenoma in the intestines.*

9. Alice McG—, aged 50, under Dr. Goodhart in 1883, with enlarged glands and a full abdomen.

Post-mortem.—The fifth and sixth ribs were matted together inside by growth, enlarged mesenteric glands. Lymphoid growths in stomach and up to pylorus, in the small intestine, and especially round ileo-cæcal valve. An enormous spleen, 44 oz., with translucent nodules.

10. Joseph B—, aged 48, under Dr. Pye-Smith in 1888, with pleuritic effusion and signs of pressure on the left bronchus. Abdomen apparently normal.

Post-mortem.—There was a most extensive lymphadenomatous overgrowth throughout the alimentary canal, involving the tonsils, stomach, and the appendix markedly. There was also infiltration of the mediastinal glands. (*See* 'Transactions' of this Society, vol. xl, p. 80.)

d. *Ten cases showing no caseation or other evidence of tubercle.*

11. John B—, aged 21, under Dr. Fagge in 1881. Three months ago typhoid fever, and an abscess formed in his thigh; three weeks later the glands began to enlarge, those in the groins, axillæ, and neck forming large masses; leucocytes increased tenfold. The right side of the face became œdematous. Frequent vomiting. Death two weeks after admission. Before death 1,830,000 red cells to c.mm., one white to 324 red.

Glands in neck, soft whitish, with hæmorrhages in spots, especially large at bifurcation of trachea.

Post-mortem.—Thymus large. Tonsils normal. Liver normal, 56 oz. Spleen, 9 oz.; normal. Behind pancreas a mass of firm yellowish-white tissue round the portal vein, adherent to its wall, and extending up to liver; to right the growth reached up to kidney; numerous enlarged glands in the lesser omentum. Kidneys, 10½ oz.; mottled on section. An anomalous case.

12. George H—, aged 9, under Dr. Mahomed in 1882.

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Petechiæ for a week. Large glands, spleen and tonsil; some increase in leucocytes; cerebral abscess in right frontal region. He died five days after admission. Enlarged glands in axillæ, groins, near bronchi, and tonsils.

Post-mortem.—Liver normal, 36 oz. Spleen, 7½ oz.; lymph on the surface, on section normal. Thymus large.

13. Arthur A—, aged 32, under Dr. Wilks in 1883. Alcoholic, no history of syphilis. Gonorrhœa in November, 1882. Glands in groin enlarged, then glands generally became enlarged, but not matted together. Enormous liver down to umbilicus; spleen not palpable; growth of glands behind naso-pharynx.

July 10th, 1883.—Paralysis right third nerve.

Under KI by August 1st the masses behind pharynx and the paralysis of the third nerve cleared up.

Admitted June 3rd; died August 27th.

Post-mortem.—Thymus large. Bronchial glands not affected. Fibroid patches in heart muscle. Spleen, 6 oz.; white nodules of growth. Large glands in naso-pharynx. Slight increase lymphoid tissue in small intestine. Liver, 88 oz.; a dense white fibroid growth occupied the middle of right lobe through whole thickness below, and only the thickness of the posterior half in upper part. Margin well defined, with raised projecting masses on surface; no juice on scraping. Cystic duct surrounded, not compressed. Numerous glands involved, none very large, none pressed on the portal fissure. The glands along the aorta and the mesenteric glands were involved; they were large, firm, succulent, and white. Right kidney mottled, with white, raised, rounded growths in the cortex more than in the pyramids; some nodules with defined margins; other infiltrate. Left kidney less involved. Glands in axillæ and groins enlarged; growth very fibrous, suggesting a syphilitic process.

14. Rachel H—, aged 29. Dyspnœa, enlarged glands. Glands on the right side of the neck enlarged in May, 1886. In December general enlargement.

Post-mortem.—Masses of enlarged glands at the root of each lung, and also in the anterior mediastinum; large dense masses of cartilaginous consistence in the mesenteric glands. Thrombus in left innominate vein. Spleen, 26 oz.; full of yellow-white

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masses one third to one quarter of an inch, but there was also a diffused growth. The mediastinal and pulmonary growths showed bands of fibrous tissue in the midst of typical lymphoid tissue. The axillary, inguinal, and supra-condyloid glands were enlarged, extremely hard, and varied in size from a hazel-nut to a walnut.

15. William V—, aged 13, under Dr. Hale White in 1893. Sore throat ten weeks, with enlarged cervical glands. Tonsils removed two weeks ago. For three days hæmorrhage from mucous membrane and skin. General enlargement of the superficial glands of the upper half of the body, but little leucocytosis. Red corpuscles 50 per cent. Liver and spleen enormous. Death from cerebral abscess, with general hæmorrhages from mucous membrane and skin.

Post-mortem.—Thymus large, 3 oz. Submaxillary and cervical glands enlarged. A calcareous nodule in one bronchial gland below the left bronchus; no other evidence of tubercle. Spleen, 29 oz., soft; infarct two inches by half an inch, pale in centre. Liver, 89 oz., contains numerous nodules of densely packed cells, round in shape, stable in character, occupying the lymphatic tracts. They form large masses in the portal areas and run in columns along the perivascular lymphatics between the liver cells. Kidneys, 12 oz.; white nodules, chiefly in cortex, the size of a walnut; no other organs showed nodular distribution. The cell infiltration runs along the lymphatics between the convoluted tubes, forming a thin sheet round them and not producing any change in the convoluted tube epithelium. No cells show any tendency to form fibroblasts, nor to any caseous change. Testicles show numerous columns of lymphoid cells running along the tubes with large interstitial hæmorrhages.

16. George H—, under Dr. Taylor.

September, 1895.—Enlarged glands in groin, axillæ and neck. Leucocytes normal in number. He died February, 1896.

Post-mortem. — Cervical glands enlarged, yellow, and of cartilaginous density. Pneumonia. Excess of lymphoid nodules in the stomach and appendix. Increase of fibrous tissue in glands, spleen, and liver. Liver also showed small-cell infiltration in the portal areas.

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17. Alfred C—, aged 16, under Dr. Pye-Smith. Sore throat; epistaxis; enlarged glands noticed on April 26th.

May 7th, 1896.—Glands enlarged in groins; popliteal spaces, axillæ; spleen and liver enlarged. Died with epistaxis on May 14th.

Inspection.—Thymus enlarged. Enlarged bronchial mediastinal glands; overgrowth of Peyer's patches and of lymphoid tissue in the colon. Liver, 75 oz., pale; white nodules and streaks. Lardaceous (iodine reaction). Spleen, 22 oz., uniform. Kidney, 19 oz.; nodular masses in cortex the size of peas projecting on surface. Extreme infiltration of small cells in lymph spaces in liver and kidneys.

18. Jane W—, aged 56, under Dr. Washbourne. Ill for two years with an enlarged spleen and glands. Coma at end. Blood examination: R = 60 per cent.; H = 40 per cent.; W. to R. 1 : 50.

Post-mortem. — Liver, 100 oz.; spleen, 61 oz.; kidneys, 8 oz.; glands enlarged.

19. Samuel C—, aged 39, under Dr. Hale White. On December 17th, 1898, he was unable to walk, and there was ptosis of the right eyelid with diplopia. His limbs were weak.

Post-mortem.—Ulcer of the stomach. In the kidneys there were nodules of lymphadenomatous tissue. The organs weighed 16 ounces.

20. Charles L—, under Dr. Hale White. For four years he has had enlarged glands on the right side of the neck, and later in his axillæ and groins.

Post-mortem.—The glands are matted together. In the lungs there are nodules a sixth to an inch across, consisting of fibrous tissue with lymphoid cells and some large cells. They are irregular in shape, softened in the centre, and may be gummatous. There are nodules in the mucous membrane of the colon, with some ulceration. The liver weighs 60 ounces, and is cirrhotic. The spleen weighs 16 ounces, and contains some large nodules, reddish brown in colour, and smaller yellowish ones. Opinions varied as to whether the lesions indicated a chronic form of Hodgkin's disease or some syphilitic fibroid process.

E. *Cases* 4 *and* 17 *gave lardaceous reaction.*

F. *In Cases* 5, 13, *and* 20 *the question of syphilis was raised.*

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29. *Avian filariasis.*

By C. W. Daniels.

The number of species of filaria in birds in tropical countries appears to be large, and each country, and to some extent each species of bird, harbours different species of filaria, though some are common to more than one species of bird.

The filaria described here are those sent to me by Dr. Kennard from British Guiana, and are, I believe, new species.

Filaria ostinops. — Definitive host *Ostinops decumanus* (Bunyah).

The parental worms, male and female, were found in the peritoneal cavity in cysts connected with the stomach.

The specimens I received were one male and one female. The female appeared to be mature, and contained embryos coiled up in eggs. It was 37 mm. in length, and the greatest diameter was 1 mm., about the middle of the worm. The head was not sharply differentiated from the rest of the worm, and was 0·05 mm. in diameter. The mouth was terminal and unarmed. The genital opening was only 0·37 mm. from the mouth, and at this point the worm was 0·3 mm. in diameter. The anal opening was 0·45 mm. from the tip, and here the worm measured 0·67 mm.; from this it tapered rapidly to the conical end, which 0·075 mm. from the tip measured 0·3 mm. Ova only were found in the uterus; some had embryos inside, so that it appears to be oviparous.

The *male* was much larger than the female, which is very unusual in this genus. There is no sufficient reason to suppose that the female had not attained nearly the full size, as the eggs were mature.

The male was 60 mm. in length. The greatest diameter was 0·67 mm., and was in the posterior half of the worm. From the cloaca, which was 0·16 mm. from the tip of the tail, there were protruded two spicules, an anterior or long, and a posterior or short spicule. Immediately anterior to the cloaca were an indistinct pair of papillæ.

The anterior spicule was protruded for 0·6 mm., and this por-

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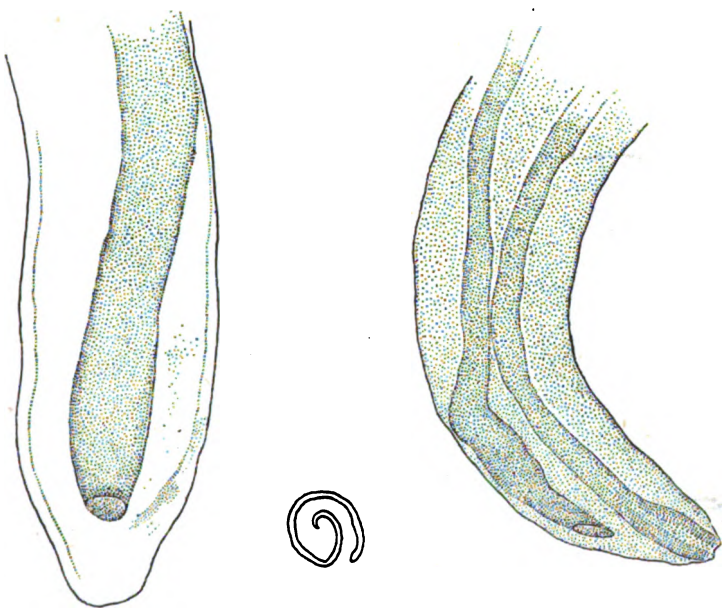
tion was continuous with the unprotruded portion, also 6 mm. in length, and which gradually increased in diameter, terminating in a trumpet-shaped expansion 0·45 mm. in diameter, into which the vas deferens appears to end. The protruded portion of the spicule has a double outline, and appears to be tubular; it was 0·015 mm. in diameter.

The second spicule was 0·65 mm. in length, and 0·14 was protruded; diameter of the protruded portion was 0·028 mm.

The embryos were small, 0·086 mm. in length, and 0·003 mm.

FIG. 22.



The tail (left hand) and head (right hand) of *Filaria ostinops*, female. In the centre the parasite is shown of natural size.

in their greater diameter. There was no loose sheath, and the tails were blunt. In the stained specimens there was a gap in the central core of nuclei 0·008 mm. in length, and rather nearer the tail, 0·03, than the head, 0·046 mm.

Filaria crotophaga.—One of the two species of filaria found in the "Old Witch," *Crotophaga ani.*

Dr. Kennard found both these species beneath the mucous membrane of the crow. In cases where the filaria were found

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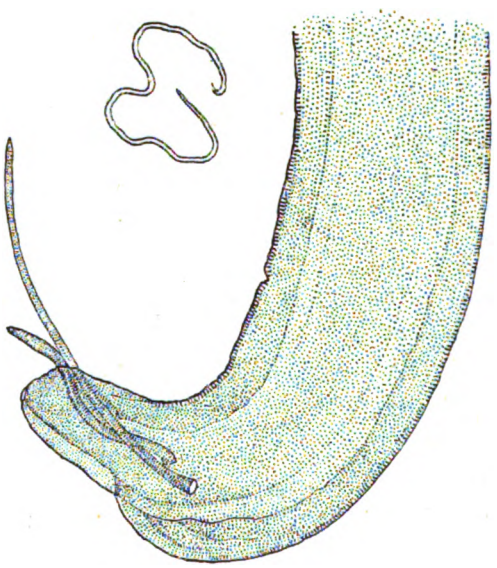
this mucous membrane was less firmly attached than usual. They were only found in birds in the wet season. No filaria were found in any other part of the body.

Filaria crotophaga (No. 1).—The female was 11 mm. in length and 0·34 mm. in its greatest diameter. At the genital opening, 0·78 mm. from the head, it was 0·31 mm. in diameter. The head was 0·049 mm. in diameter; the mouth was terminal and unarmed, and from it led a short œsophagus 0·04 mm. in length, ending in a marked dilatation. The anal opening was 0·22 mm.

FIG. 23.



Tail of *Filaria ostinops*, male. Above is shown the parasite of natural size.

from the tip of the tail, and at this point the diameter was 0·15 mm.

The male, identified as being the male of this species by the short œsophagus, was 7 mm. in length. The greatest diameter was 0·75 mm. The head was 0·004 mm. in diameter, and from the terminal unarmed mouth was an œsophagus 0·048 mm. in length. The cloacal opening was 0·109 mm. from the tip of the tail; two spicules, an anterior and posterior, were protruded.

The anterior spicule was the longer, and in all was 0·94 mm. in length. Its tubular nature was shown by the fact that almost

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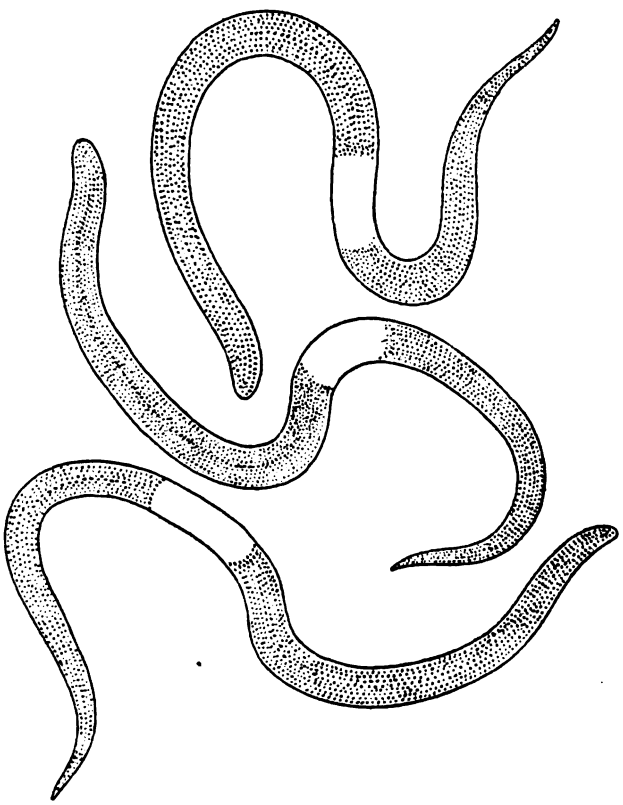
its whole length was occupied by an air bubble; 0·27 mm. were protruded, and this portion was 0·013 in diameter. The spicule was continued along the axis of the worm, and terminated in a trumpet-shaped expansion 0·026 mm. in diameter. The air bubble extended well into this trumpet-shaped expansion.

The posterior spicule was protruded for 0·09 mm., and was in

FIG. 24.



Filaria ostinops, embryos.

close contact with the anterior, which it appeared to support and partially enclose. The whole arrangement closely resembles that in *Filaria bancrofti*, and the incident of the tube being filled with air, as showing the continuity of the trumpet-shaped expansion into which the vas deferens opens with the protruded spicule, renders it probable, as has been surmised before, that in function the anterior spicule is truly penile. There were three

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papillæ (? pairs) anterior to the cloaca and one posterior. The cuticle was thickened at the tip of the tail so as to form a pointed extremity. The second species of filaria found in the *Crotophaga ani* I propose to call *Filaria kennardii*, after Dr. Kennard, who found these specimens.

These filaria were rather longer than the first, and there were two females and one male sent to me.

The females were 18 and 19 mm. in length, and the greatest diameter was 0·1 mm. The head was unarmed and the mouth terminal. In diameter it was 0·023 mm., and there was a slight constriction behind it—the neck. Traced backwards it steadily increased in diameter, and 0·16 mm. from the head measured 0·046 mm. The genital opening could not be clearly distinguished, but seemed to be about 0·2 to 0·25 mm. from the head. The eggs were much longer than they were broad (0·033 × 0·009 mm.), and were arranged in a great extent at right angles to the long axis of the worm.

The anal opening was 0·13 mm. from the tip, and there the worm was 0·046 mm. in diameter; it rapidly tapered to a rounded blunt tip 0·01 mm. in diameter. There was very slight cuticular thickening at the tip.

The male was 12 mm. in length, and the greatest diameter was 0·25 mm., but the specimen was a good deal damaged, and this measurement is probably in excess of the true measure. The head, also much compressed, measured 0·06 mm.

The tail end is comparatively little injured. There were two spicules, an anterior and a posterior; both partly protruded. The long anterior spicule is protruded for 0·4 mm., and the remaining portion is at least as long, but the termination is injured. In diameter the protruded portion is 0·018 mm., gradually tapering to the tip. The posterior spicule is protruded for 0·21 mm., and is 0·015 mm. in diameter, tapering to a sharp point. This spicule is much curved. The cloaca from which these spicules are protruded is 0·15 mm. from the tip of the tail, and the diameter of the worm at this point is 0·084 mm. There are two papillæ just in front of the cloaca, and one posterior near the tip of the tail.

Two species of embryos were found in the blood of this bird, but it is impossible to state which embryo corresponds to each parental form.

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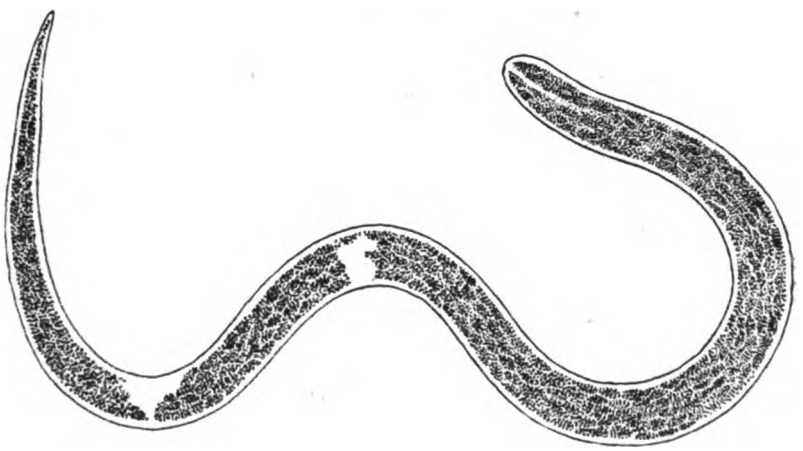
Both embryos are destitute of a loose sheath. They are small stumpy worms which taper abruptly to sharp tails. They differ in size, in the arrangement of the nuclear core, and the intensity with which they stain. The one which stains most deeply is 0·0495 mm. in length and 0·0045 mm. in diameter. There is an incomplete break in the nuclear core 0·0285 mm. from the head, and another much smaller one 0·009 mm. from the tail.

The other, which stains faintly, has no decided gaps in the nuclear core. It is 0·063 mm. in length and 0·0045 mm. in diameter.

Embryos were found by Dr. Kennard in three other birds, but the adults were not found by him.

FIG. 23.



Filaria crotophaga, embryo.

In *Eugyptila rufaxilla* (Ground Dove) a large filarial embryo with a loose sheath was found. The embryo varies from 0·220 to 0·250 mm. in length, and is 0·006 in breadth. The sheath is about 0·09 mm. longer than the embryo. The tail is sharp; there is a small gap 0·04 mm. from the head in the nuclear core, and there are other irregularities in the arrangement of the nuclei which do not seem to be constant.

In a species of parrot, filarial embryos 0·185 to 0·200 mm. in length and 0·007 in breadth were found. There is a gap in the nuclear core 0·042 mm. from the head. The tail is sharp and tapers slowly. There is a loose sheath. This filarial embryo is usually much contorted.

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In the "mocking-bird" the embryos are of two distinct species, without intermediate forms. One of them resembles that of the Bunyah, in that there is a large complete gap in the nuclear core. It is 0·08 to 0·09 mm. in length, 0·004 mm. in breadth, and the nuclear gap is 0·004 mm. in length and 0·03 mm. from the blunt tail. There is no sheath. The differences in the measurements are so slight, and the nuclear arrangement so similar, that it is possible that it is the same embryo as that of the Bunyah.

The second embryo is sheathless, and has a blunt tail, but has no complete nuclear gap. It was 0·12 mm. in length, 0·0045 in diameter; the tail is quite blunt, and measures at the tip 0·0015 mm. The nuclear gap is large but incomplete, and is situated 0·046 mm. from the tail. The embryo stains less readily than the other in the same blood.

The examinations made are those of the dried and stained embryos. The adults had been passed through several strengths of alcohol, and in most cases were good, but the measurements are probably below those of the fresh worms.

A filaria found by me in a blue jay, species undetermined, in India, presents many points of difference from these filaria. The adults were found in the loose connective tissue beneath the skin in the anterior part of the neck.

The female was 48 mm. in length, and in its greatest breadth was 0·9 mm. The head was 0·14 mm. in diameter, and the mouth was terminal and armed with a pair of papillæ. The mouth was rather wide, 0·03 mm., but narrowed rapidly into the straight œsophagus, 1·5 mm. in length. The œsophagus terminated abruptly in a thick-walled intestine. The intestine was nearly straight, and terminated in an anus 0·3 mm. from the tip of the tail. At the anal orifice the diameter of the worm was 0·25 mm. There was a cuticular thickening at the tip of the tail.

The vaginal outlet was 0·6 mm. from the head. It was by a small papilla, in the centre of which was the orifice of the vagina. The vagina was a narrow tube 0·01 mm. in diameter, with thick muscular walls 0·04 to 0·05 mm. in thickness. The tube was dilatable, as in one specimen eggs were found in part distending it.

The vagina in its narrow part was 0·6 mm. in length, and the

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tube then widened out into a comparatively thin-walled sac distended with ova, and into this sac the two ovarian tubes opened together. The eggs in the vaginal sac were 0·073 mm. by 0·043 mm., and each contained a coiled-up embryo 0·150 mm. to 0·165 mm. in length, and 0·009 in thickness. The whole arrangement of narrow tubular outlet from a dilated vaginal sac closely resembles that described by me for *Filaria Bancrofti* in the 'British Guiana Medical Annual,' 1896. In the blood embryos of many sizes were found, varying from 0·06 to 0·21 mm. in length. Intermediate forms occur, but most of the embryos were near one or other size. The arrangement of nuclei differs in the small and large, but the nuclear arrangement varies in embryos *in utero* and in older worms in other species. Whether this oviparous filaria discharges its ova into the connective tissue, and the embryos then escape and undergo certain changes in the blood, or that there were two distinct species, and the parental forms of one were overlooked, cannot be stated definitely.

The males were 26 mm. in length and 0·7 mm. in breadth at their greatest thickness. Breadth of head was 0·12 mm. The œsophagus was 1 mm. in length, and otherwise the alimentary canal resembled that in the female. The cloaca was 0·15 mm. from the tip of the tail, and from it protruded two *lateral* spicules.

These spicules were equal and flattened from side to side, 0·08 were protruded, and the total length was 0·27 mm. There was no indication of a tube, and they did not end in trumpet-shaped expansions internally.

These lateral spicules I believe to be merely claspers, and not representative of the anterior spicules found in the other filaria, and not to be penile in function.

In life they remained out of the body, and no retraction or further protrusion took place, whilst in filaria with unequal anterior and posterior spicules alternate protrusion and retraction of the spicules independently of each other takes place.

No representative of the spicules of the other class was found, and the opening of the cloaca was between the two lateral spicules. There was a thickened cuticular cap over the tip of the tail. There were no papillæ.

There are many points of interest in connection with avian

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filariasis. The great variety of species, the variability of the place in which the parent worms are found, and the absence of any knowledge as to the intermediate hosts are of considerable importance.

The three species sent by Dr. Kennard were all found in the neighbourhood of the alimentary canal, and it is noteworthy in this connection that two of the human filaria, *F. perstans* and *F. Demarquayi*, have only been found near the human alimentary tract. These two species do not appear to be conveyed by mosquitoes, and it is quite possible that alike some of the human and some of the avian filaria are taken in *viâ* the alimentary canal. *February 4th*, 1902.

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30. *The identity of the* Bacillus Gärtner *with the rat bacillus of Danysz.*

By E. Klein, F.R.S.

It is well known that the bacillus (enteritidis) of Gärtner is a variety of *Bacillus coli*, having with this latter a number of characters in common, while in some other respects it differs from the *B. coli communis*. The Gärtner bacillus in plate cultivation, in streak and stab culture, in size and shape, and in not liquefying gelatine, in forming gas in streak and gelatine culture, in giving a positive result with neutral red, and in culture on potato is identical with *B. coli communis;* but it differs from this in not curdling milk, in producing at first acid then slight alkali, in not producing indol in broth culture, in being very motile and possessing numerous flagella, and in being virulent for rodents. Having had the opportunity of studying the bacillus described by Danysz as of particular virulence to rats, and known as the Danysz rat bacillus, I was struck by the remarkable identity in respect of all the above characters—morphological, cultural, and experimental—between the Gärtner and Danysz bacillus. This seeming identity was still further confirmed by observations made as regards the agglutination of

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these two bacilli by sera of animals previously immunised by either of them.

A number of experiments were made in this direction, viz.: (1) Guinea-pigs were immunised against an otherwise fatal dose of the Danysz bacillus by previous repeated subcutaneous injections of small subfatal doses of living culture of the Danysz bacillus. The blood-serum of such animals was tested on emulsion of Danysz bacillus, and was found to have distinct agglutinating action in dilutions up to 1 in 200 within fifteen minutes. The same blood tested in the same dilutions on emulsion of Gärtner bacillus exhibited exactly the same agglutinating action. (2) Guinea-pigs were immunised against an otherwise fatal dose of Gärtner bacillus by previous repeated subcutaneous injections of small subfatal doses of living culture of the Gärtner bacillus. The blood-serum of such animals was tested on emulsion of Gärtner bacillus, and was found to have distinct agglutinating action in dilutions up to 1 in 300 within thirty minutes. Tested on emulsion of Danysz bacillus, this same blood-serum had the same agglutinating action. (3) Guinea-pigs immunised against Danysz bacillus were found to be immunised also against an otherwlse fatal dose of Gärtner bacillus; and (4) guinea-pigs immunised against Gärtner bacillus were found immunised against an otherwise fatal dose of Danysz bacillus.

From all these facts it follows that both the Danysz (rat) bacillus and the Gärtner (enteritidis) bacillus are in all respects identical except in regard to their derivation, and that both appear to be the same variety of *Bacillus coli.*

November 19th, 1901.

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31. *On the pathological effects produced on the central nervous system by thyroid excision and by thyroid feeding.*

By Walter Edmunds.

[With Plate X.]

The observations are based on twelve experiments, three on monkeys and nine on dogs.

Of the monkeys, one was subjected to total excision of the

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thyroid and parathyroids; from the effects of this operation the animal died in 112 days. The other two monkeys were fed with very large doses of a thyroid preparation (thyro-colloid); one died in seven, the other in twelve days.

Of the dogs, three were subjected to primary total excision of the thyroid and parathyroids; they all had severe symptoms in consequence, and died (or were killed) in three, six, and twelve days. One underwent partial excision of the thyroid; this was followed by chronic symptoms of which he died in 329 days. Two others also underwent a partial excision operation, but, in addition, the nerves supplying the portion of thyroid left were divided with a view to paralysing the secretory function of the thyroid and parathyroid; these two dogs died in 242 and 271 days. In three dogs similar operations were performed, but were followed at a later date by operations completing the total excision of the thyroid.

By kind permission of Dr. Mott, the material was examined at the Pathological Laboratory of the Claybury Asylum; the Nissl and other methods of preparation were used.

In all cases pathological changes were found, but they varied much in degree in the different experiments; the changes were most marked in the two monkeys which died from thyroid poisoning.

The changes found consisted in chromatolysis of the cells, large and small; swelling of the cell bodies; swelling of the nuclei; extrusion of the nucleus; and total destruction of the cell body, leaving only a practically free nucleus.

As two of the monkeys underwent no operation, and the other monkey and three of the dogs survived their respective operations several months, any possibility of the appearances being complicated by microbic infection from a recent operation wound is in these cases excluded; all the operation animals died (or would have died if they had not been killed) from the specific symptoms produced by thyroid operations.

A description of the experiments and of the pathological conditions found is appended.

Monkey A.

The monkey was subjected to total excision of the whole of the thyroid and parathyroids.

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Thirteen days after the operation it was noticed that the eyes were narrower than before operation. Thirty-eight days after the operation there was an attack of convulsions with loss of consciousness lasting an hour. Seventy days after operation the eyes had become very narrow. One hundred and twelve days after operation the monkey had become so weak and ill that it was well to kill him.

Cortex.—Most of the small pyramidal cells are affected, some almost entirely destroyed, very little being left of the body of the cell, and practically only a free nucleus remaining. Some of the cells are affected in a less degree, the change consisting in (1) destruction of the processes of the cells; (2) more or less complete destruction of the body of the cell; (3) swelling of the nucleus. Some of the cells are very little, if at all, affected. The medium-sized and larger pyramidal cells are similarly affected, but the changes are not so advanced. The vessel walls are a little thickened, showing some proliferation of the adventitial and endothelial nuclei, especially in the arterioles and capillaries, but these changes are not at all pronounced. The vessels are slightly congested. There is slight leucocytosis and some proliferation of the neuroglia.

Medulla.—The motor cells show slight swelling but no material changes.

Cord.—The changes in the large cells are more advanced than in those of the medulla, and show chromatolysis; a few of the cells are destroyed: further, there is more glial proliferation in the cord than in either the cortex or medulla. The vessel changes are about the same as in the cortex.

Monkey B.

The monkey was fed with very large doses of thyro-colloid. During the first few days the monkey did not seem to be seriously ill, but on the fifth and sixth days of the treatment his eyes were noticed to be wider than before treatment, and he died on the seventh day.

Cortex.—Most of the cells show very advanced changes—the processes are lost, chromatolysis is very advanced, the cell body broken down so that many practically free nuclei are seen.

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These changes are most marked in the smaller cells. There is a considerable amount of cellularity about the vessels, which are also congested. The pia mater is slightly thickened, and its vessels congested. There is also glial proliferation and leucocytosis throughout the cortex.

Medulla.—Many large motor cells completely destroyed; the smaller cells are much less affected. The vessels of the medulla are considerably congested. There is also leucocytosis and glial proliferation.

Cord.—Most of the large cells of the anterior horns have undergone great chromatolysis, and are practically destroyed.

Monkey C.

This monkey was fed on large doses of thyro-colloid. He only had marked signs of illness on the twelfth day, and on that day he died.

Cortex.—The great majority of the cells show advanced acute changes. Both the cell body and the nucleus are swollen, and there is marked chromatolysis, especially at the edge of the cells. Many cells are much broken down; the smaller and medium-sized pyramidal cells are the most affected. There is a moderate amount of congestion of the vessels of the pia mater and of the cortex generally; also some leucocytosis and some glial proliferation.

Medulla.—Many of the cells show advanced degenerative changes, much chromatolysis, with breaking down of the body of the cell and extrusion of the nucleus. Some cells are more affected than others.

Cord.—All the cells show very advanced changes, much chromatolysis, breaking down of the body, and extrusion of nucleus. No healthy cells to be seen.

Dog A.

Total excision of the thyroid and parathyroids was performed.

The second day after the operation the dog seemed well. The third day he seemed extremely weak and ill, and was, in fact, obviously dying. He was therefore anæsthetised and bled to death.

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Cortex.—Betts's cells are swollen, and the nucleus also is swollen and pale. (This is a condition which is recoverable from if the animal lives.) There is also well-marked chromatolysis. Some few cells show further destructive changes. The smaller cells show much more swelling and breaking down of the cells. There is enormous congestion of the vessels and much leucocytosis, and at one place a hæmorrhage under the pia mater. Many of the small cells appear to be vacuolated; these changes appear to be due to œdema of the cells.

Medulla.—An enormous number of the cells are affected; the cell body and nucleus are swollen. There is advanced chromatolysis. In some cells the stainable substance has almost entirely disappeared; the cells, however, retain their processes, and there appears to be little destruction of the reticulum of the cells. There is enormous congestion of the blood-vessels.

Cord.—The changes in the cord are the same as those in the medulla, but are not quite so advanced. Some part of the cord was prepared by the Marchi process. The cord shows throughout the sections scattered degenerated fibres, but the changes are most marked in the ganglia of the posterior root.

Dog B.

Total excision of the thyroid and parathyroids was performed.

On the fifth day it was noticed that the dog was extremely weak, slow gait, eyes narrow, and eyeball receded. On the sixth day the dog was killed.

Cord.—Cells are little altered except that they are swollen and show early signs of chromatolysis. Cells in this condition are capable of recovery if the cause be removed.

Dog C.

Dog underwent total excision of whole thyroid apparatus. The usual symptoms appeared. On the eleventh day an attack of convulsions came on; he recovered from these, but his gait was very staggering. The twelfth day he was killed.

Cord.—The majority of the cells are somewhat swollen and show early chromatolysis; some few cells show more advanced changes; some cells show marginal chromatolysis.

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Dog D.

The whole of the right lobe of the thyroid was removed, and also nearly the whole of the left lobe, leaving, however, one parathyroid and a small portion of thyroid proper.

A month after this operation it was noticed that the eyes were narrower and somewhat sunken (enophthalmos). Seven months after operation the gait was affected, owing to rigidity of the hind limbs; a month later tremors were added to the other symptoms. Dog gradually became worse, and was killed 329 days after operation.

The thyroid portion left was found *post mortem*, but was unfortunately lost before it was microscopically examined.

Cord.—The changes shown are only slight. There is slight chromatolysis, absence or diminution of the Nissl bodies in the processes of some cells, some swelling of the nuclei of the cells, and the cell bodies abnormally plump.

Dog E.

Removed a length of the right superior laryngeal nerve, and also of the right vagus at the level of the thyroid lobe; also excised the left thyroid lobe with its parathyroids.

Three months after operation the dog had obvious tremors, a stiff gait with his hind limbs, a difficulty in rising from a sitting posture, and chronic priapism. Two months later these symptoms had passed off. Six weeks later the tremors and stiffness in the hind limbs had reappeared, and they persisted and gradually became worse till the death of the dog 271 days after the operation.

Cortex.—Many of the smaller pyramidal cells have practically disappeared, nothing but free nuclei being left; the medium-sized pyramidal and Betts's cells also show very advanced changes, there being marked destruction of the cellular reticulum. There is very marked congestion of the vessels of the pia mater and of the cortex. There is considerable thickening of the pia and of the vessels in the cortex, and also a good deal of leucocytosis.

Cord.—Upper part: some few cells are fairly healthy, or show only slight changes; others are seen in all stages of

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degeneration. Also a good deal of congestion and thickening of the membranes. Lower part: same as upper part.

Dog F.

Excised a length of right superior laryngeal nerve; also a length of right vagus at level of the thyroid; also the whole of left thyroid lobe.

Thirteen days after operation, loss of flesh and tremors. Thirty-eight days after operation, in addition to above, instability of gait; a month later these symptoms recovered from. Five months after operation dog is stupid and dull; no tremors now. Seven months after operation extreme emaciation; no tremors; some affection of gait. Dog killed.

Cortex.—There are scattered foci in which there is considerable destruction of small pyramidal cells; in other areas, however, these remain fairly normal. The medium-sized and Betts's cells are comparatively little affected; some show slight swelling and chromatolysis. The vessels are not much congested.

Medulla.—Shows very similar changes to the cortex.

Cord.—Similar changes to those in cortex, but only slight.

Dog G.

Excised length of right superior laryngeal nerve; also of right vagus at level of thyroid; also the whole of left thyroid lobe.

A fortnight after operation, tremors and loss of flesh. Seventeen days after operation, excision of right thyroid lobe. On microscopic examination the vesicles of the lobe were seen to be full of cells, taking the place of the colloid. A week after second (completing) operation, tremors and affection of gait. Fifteen days after second operation, an attack of convulsions; dog extremely ill; killed.

Cord.—The majority of the cells show swelling and some chromatolysis; a few cells show more advanced destructive changes.

Dog H.

Excised a length of the right superior laryngeal nerve; also a length of the right vagus opposite the thyroid; also the whole of the left thyroid lobe. This was followed in a few days by tremors.

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Twenty-seven days after operation, excision of the remaining (right) thyroid lobe: on microscopic section about normal.

The second (completing) operation was followed by the usual symptoms, and on the fifth day the dog was killed.

Cord.—The majority of the cells are practically normal, but some show swelling and chromatolysis; a few cells appear to be destroyed.

Dog J.

The whole of the right lobe and the greater part of the left lobe of the thyroid was excised, leaving only a parathyroid and a small amount of thyroid proper on the left side. This was followed in a fortnight by tremors, which, however, passed off in a few days.

Three months after operation a second operation on left superior laryngeal nerve and left vagus was performed with a view to interfering with the innervation of the portion of thyroid and parathyroid left. This operation produced no effect.

A month after second operation the remaining parathyroid and portion of thyroid was removed. Microscopically the parathyroid was found normal, and the thyroid portion showed absence of colloid, its place having been taken by a watery secretion; the secreting cells normal, and the lining membrane not folded. This operation was followed by the usual symptoms, and the dog died in three days.

Cord.—The large motor cells show early chromatolysis; the smaller cells are more broken down. Most of the cells show early chromatolysis; some few are almost normal. There is considerable congestion of the vessels.

REFERENCE.

Otto Maas.—'British Medical Journal,' "Epitome," September 28th, 1901.

March 18th, 1902.

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DESCRIPTION OF PLATE X,

Illustrating Mr. W. Edmunds' communication on the Pathological Effects produced on the Central Nervous System by Thyroid Excision and Thyroid Feeding. (Page 343.)

The drawings, which were made by Mr. Lapidge, are from specimens prepared by Nissl's method; the magnification is 600 ($\frac{1}{12}$ oil immersion).

Fig. 1.—A motor cell from the spinal cord of Dog G; the Nissl bodies are normal and well marked.

Fig. 2.—From the spinal cord of Monkey A. The greater part of the body of the cell has been destroyed.

Fig. 3.—A cell from the cortex of the brain of Dog F. Most of the Nissl bodies have disappeared, showing the empty reticulum of the cell.

Fig. 4.—From the spinal cord of Dog C. Considerable chromatolysis of the Nissl bodies has occurred, and some of the processes of the cells are broken off.

Fig. 5.—From the spinal cord of Monkey C. The Nissl bodies have almost entirely disappeared, showing the reticulum of the body of the cell.

Fig. 6.—From the spinal cord of Dog E. The Nissl bodies have disappeared, and one of the processes of the cell is destroyed.

Fig. 7.—From the spinal cord of Monkey B. The Nissl bodies have completely disappeared; the cell processes and part of the cell body are destroyed.

Fig. 8.—From the spinal cord of Dog E. This cell and that shown in fig. 6 are from the same section; they show that the appearances are not accidental.

Fig. 9.—From the medulla of Dog A. Chromatolysis has occurred, and the cell processes are broken off.

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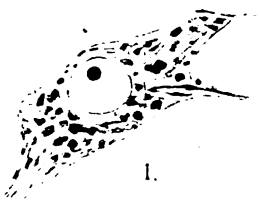

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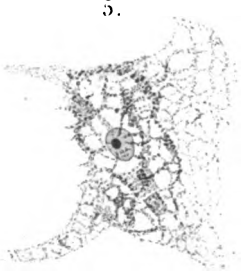

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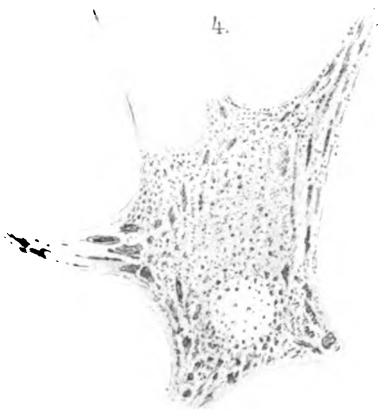

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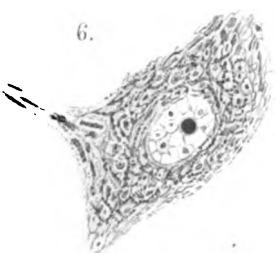

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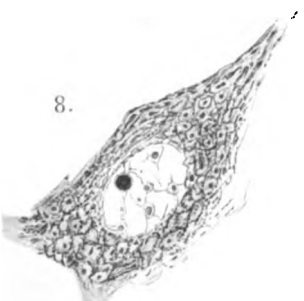

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32. *A case of hydatid disease of the gall-bladder* (?).

By LAWRIE HUGH MCGAVIN.

THE following case of hydatid disease of the gall-bladder having recently come under my notice, I have been tempted to record it as an example of what is, I think, generally acknowledged to be a distinctly rare condition.

The patient was a married woman, 32 years of age, who was transferred to my care in the Hospital for Women, Soho Square, by my colleague Dr. James Oliver, with the following history:— Until fourteen years of age she had been perfectly healthy, but at the age of sixteen years she suffered somewhat from anæmia (she stated that she had "inflammation of the womb"), and shortly afterwards, after suffering some difficulty and pain during micturition, she passed certain bodies resembling "grapes with the stalks removed," which her medical attendant told her must have come from the uterus. Of these bodies she passed one more at the age of seventeen years, and one at the age of nineteen years. No examination appears to have been made of these. She had never been abroad, nor had her employment in any way been such as to have suggested the probability of echinococcus ingestion. In April, 1898, she had a miscarriage, and during the subsequent bandaging she noticed a mass in her abdomen, which she showed to her medical attendant. It appears to have caused her no trouble until May, 1900, when she had a sudden attack of vomiting, accompanied by severe abdominal pain, and from this time the mass was tender on pressure and was accompanied by a feeling of nausea. She had no further vomiting, but in August the attacks of nausea became more frequent, lasting two or three days at a time. From this time the tumour began to increase in size and continued to grow, accompanied by increasing nausea and pain. These attacks bore no relation to her meals, but appeared to be more usual towards evening. She had never suffered at any time from jaundice, and her stools had always been normal in colour. She stated that she had lost weight

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considerably, but, as no definite record was kept, this was, I think, fallacious.

The case was seen by Dr. Oliver and myself in consultation on April 25th, 1901, when the following condition was found:— Outwardly the abdomen was quite normal in appearance, no swelling being visible. On palpation the recti abdominis were felt to be separated by about an inch; and lying slightly to the right of the middle line and about an inch above the umbilicus was a hard, slightly lobulated, roundish mass, which seemed to be rather flat than globular. It was freely movable, especially laterally to the right, although it could be brought beyond the middle line to the left. In consistence it was hard, but not to a very marked degree; elasticity could not definitely be made out. On percussion it was dull, and there was impaired resonance between it and the liver, which was not enlarged. On pressing the tumour the patient complained of nausea, and on increasing the pressure of some pain in the epigastrium. As far as could be judged, the tumour measured about three inches each way, and was not apparently connected with the liver. In the absence of jaundice, colic, and clay-coloured stools, and from the very free mobility of the tumour, a diagnosis of carcinoma of the omentum was made, and I advised an exploratory laparotomy, which was undertaken on May 2nd.

On opening the abdomen in the linea alba I found a large whitish mass measuring about three inches by five, having several flat prominences on its surface, of rather hard consistence suggesting nodules of growth, in the situation of the gall-bladder. To this mass the great omentum was adherent in front, the edge of the liver was spread out over it above, and the transverse colon was in a similar condition below. The tumour was found to be the gall-bladder itself, and the position of it, so near the middle line, was accounted for by the fact that the liver was much more movable than is usual, although the other viscera showed no marked degree of enteroptosis. Under the impression that I had to deal with a primary carcinoma of the gall-bladder I freed the organ without much difficulty, ligatured and divided the cystic duct (the lumen of which was then seen to be completely obliterated), and removed the gall-bladder. On opening it no fluid exuded, but it was found to be lined by a thick blanket of hydatid membrane unstained by bile-

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pigment and which peeled away with extreme ease, the cavity of the cyst being occupied by numerous daughter cysts and gelatinous semi-translucent material. I then examined the other viscera for indication of more cysts, but I was unable to find any tumour or enlargement which might point to such, and, although time may prove to the contrary, I am strongly of opinion that in this case the gall-bladder alone was affected.

The rarity of hydatid disease affecting the gall-bladder, either solely or in conjunction with other organs, may be judged of from the small number of cases at present recorded. I have been unable to find more than three cases recorded in the last twenty years. The first is that mentioned by Dr. Bowman,[1] in which the patient died during aspiration of a hydatid cyst of the lung. The gall-bladder was found *post mortem* to be distended by a single cyst of the size of a fœtal head containing one daughter cyst. There had been no signs of jaundice, nor was pain at any time present. In the second case, reported by Mr. J. Knowsley Thornton,[2] the symptoms of acute biliary colic were present; they recurred once, and were then followed by jaundice and choluria. Here the gall-bladder contained a number of hydatids and much bile-stained fluid, the cystic duct being patent, and one other cyst was removed from the omentum. The third case is reported by Mr. Frederick Page,[3] the symptoms being chiefly vomiting and epigastric pain. A tumour was felt, and on aspiration yielded perfectly colourless fluid. Cholecystotomy was performed, and the organ was found to contain a single cyst without daughter cysts, the cystic duct being patent. Mr. A. W. Mayo Robson[4] mentions a case of hydatid disease simulating gall-stone attacks in which hydatids appear to have been discharged from the liver into the bile-ducts, infective cholangitis being the result. But here the disease appears to have originated in the liver. The same author draws attention to certain cases, all of which appear either to have originated in the liver or to have been complicated by communications between the liver and gall-bladder, leaving the original site of the disease in doubt.

[1] 'The Lancet,' April 8th, 1876, p. 532.
[2] Ibid., April 4th, 1891, p. 763.
[3] Ibid., April 9th, 1898, p. 995.
[4] 'Diseases of the Gall-bladder and Bile-ducts,' pp. 42, 43.

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With regard to the diagnosis of hydatid disease of the gall-bladder, I am unaware of any case having as yet been diagnosed before operation. The difficulties in the way of making such a diagnosis are obvious, and beyond the recognition of a tumour as being the gall-bladder in a state of distension (presuming always that no other swellings exist), I doubt if a definite diagnosis is possible. As to the treatment of such cases, it must necessarily be considered from the special aspect of each individual case. In my own case cholecystectomy would have been clearly indicated (the cystic duct being no longer patent and the mucous membrane completely destroyed by pressure) even had the case not been considered one of malignant disease. The patient, I may say, has made an uneventful recovery. The specimen is now in the Museum of the Royal College of Surgeons. *October 15th*, 1901.

Report on Mr. McGavin's specimen of hydatid cyst.—The cyst in question is of oval form, about four inches in its chief diameter, and varies in thickness, measuring, where thickest, three millimetres.

It is regarded by the exhibitor as the gall-bladder for the reason that it occupied the position of that structure, that nothing representing the gall-bladder was seen when the parts were exposed during life, and that what was taken to be the obliterated cystic duct was ligatured in the removal of the cyst. By this we understand the author to imply that the cavity of the cyst is the proper cavity of the gall-bladder.

To the naked eye the tissue of the cyst wall is homogeneous except for traces of concentric striation, most obvious where the wall is thickest; here and there it is streaked with white, opaque patches, but is nowhere so calcified as to resist the knife, and in consistence is as firm almost as cartilage. The inner surface is rendered irregular by the projection of low flakes of a firm, closely adherent material.

Of the cyst wall we have studied sections from different parts, and we may briefly describe their common histological appearances, for they do not differ in any essential respects.

Sections made at right angles to the surface exhibit most outwardly a zone of dense lamellar fibrous tissue, with flattened, sparsely distributed connective-tissue cells in its

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clefts. The lamellæ are freely interconnected, though remarkably regular and parallel in disposition, and under a high power they present a fine secondary fibrillar structure. Towards the inner aspect the tissue, though of the same character, has undergone necrosis, and presents no cell elements. Most internally the lamellar material gives place to an irregularly fissured hyaline-looking substance devoid of cells, which forms the actual inner surface of the cyst. In this there occur irregular groups of calcareous granules taking the hæmatoxylin stain; examination with a twelfth shows that the groups do not correspond with any formed elements, such as muscle-cells, but lie free in the homogeneous material.

Besides these calcareous foci there are others in the more internal of the underlying strata of the lamellar tissue. In these the calcareous substance appears in the form of delicate interconnected lines, stained with the hæmatoxylin, and corresponding with the course of certain of the secondary fibrils of the lamellæ, in connection with which they can be observed to arise.

There is nowhere any structure resembling that of muscle-fibre. Not only is this true of the longitudinal sections of the bundles or lamellæ, but in the oblique and cross sections the divided area is in all instances resolvable into a close set of fine points corresponding with the secondary fibrillæ of the primary fibres.

We do not, therefore, think that the cyst under consideration is the gall-bladder. It resembles in structure the thick cysts formed round hydatids in other situations, as described by one of us in the 44th vol. of the Society's 'Transactions,' p. 151 ("Lamellar or Corneal Fibroma").

In our opinion the cyst has probably arisen in the subperitoneal tissue on the under aspect of the liver in the situation of the gall-bladder. The gall-bladder, on this view, would be compressed by the contiguous growth of the cyst. The outer surface of the cyst is firm to the touch and uniform in appearance, and nowhere offers any indication that an empty and atrophied gall-bladder occupies any part of it. Incisions made in situations where eminences suggest the remains of a gall-bladder show only the same dense fibrous tissue such as exists elsewhere.

We are thus inclined to suppose that the atrophied remains of

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the proper gall-bladder have been left behind, compressed against and adhering to the under aspect of the liver, and that in this way they may have escaped recognition at the time of the operation. At neither pole of the cyst is any structure resembling a cystic duct discoverable.

H. D. Rolleston.
S. G. Shattock.
(Signed) D'Arcy Power, Chairman;
on behalf of the Members of Council representing the Section of Morbid Anatomy.

33. *A case of multiple osteoma associated with chondrosarcoma of the ribs.*

By L. H. McGavin.

The case from which the two specimens exhibited were removed *post mortem* was admitted to Guy's Hospital on February 18th, 1901, under the care of Mr. Arbuthnot Lane, to whom I am indebted for permission to publish it.

The patient, a man aged 33 years, had always been in good health till four years previously, when a small lump appeared on the chest wall in the right axillary line. This lump grew larger gradually, and he therefore consulted his medical adviser, who told him he had some form of mammary tumour. He then went to Leicester Infirmary (February, 1900), where the tumour was removed. The wound never healed, and he accordingly was readmitted in October, 1900, and the part treated by scraping. The mass recurred, and seven weeks later erosion was again resorted to. The discharge from the wound now became very foul and profuse, and he therefore came into Guy's Hospital. The report made to me from Leicester Infirmary stated that the tumour was a chondrosarcoma.

On examination.—The patient's right pectoral region was occupied by a mass of growth, the extent of which was limited on the surface in front by the nipple line, behind by the post-

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axillary line, below by the sixth intercostal space, while its limits above were indefinite. A wound, that of the old operation, occupied the centre of the mass, and from this exuded foul pus and sero-purulent fluid; and on making the patient cough or strain air was expelled with a distinct hiss. The pectoral and axillary glands were hard and markedly enlarged.

The patient exhibited a condition of multiple exostoses to a remarkable degree; his knee-joints were both surrounded by large bony masses, many of which suggested ossification of the tendons about the joints. The upper ends of the tibiæ were also much enlarged, that of the left side being the most marked. The lower ends of these bones were in a somewhat similar condition, and one or two prominences were present at the lower ends of the fibulæ.

After a sojourn of three weeks in hospital, during which erosion of the mass was unsuccessfully attempted, the patient died with all the signs of solid lung. The following is an abstract of the report of the autopsy:

"The mass extends in front to the middle line, upwards to the second rib, backwards as far as a line drawn through the post-axillary fold. The opening into the chest has walls formed by bony projections, and leads into a cavity measuring 9 cm. by 6 cm., the upper and posterior part being formed by a firm mass of growth which is firmly adherent to the upper lobe of the right lung.

"The cavity has projecting into it in all directions irregular plates of bone. Right lung compressed and airless, especially the upper lobe; left lung œdematous. Bronchial glands enlarged; left pleura covered by old adhesions; *ante-mortem* clot in the branches of the left pulmonary artery.

"The projections on the tibiæ have a bony base and are covered by cartilage."

I have brought these specimens before the Society for two reasons:—Firstly, the size of the bony outgrowths and their number, especially in such a circumscribed area, are, I think, very unusual; I have been unable to find any other specimen so remarkable in this respect. Secondly, the association of chondro-sarcoma with multiple exostoses is apparently an exceedingly rare event.

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Bland-Sutton, in his work on tumours,[1] mentions a case reported by Otto Weber[2] "of numerous symmetrical exostoses of the long bones of the upper and lower limbs, the ribs, and scapula in a man aged 25 years. A chondro-sarcoma arose in the right hip bone and attained enormous proportions. It perforated the left external iliac vein, and pieces of the tumour, detached as emboli, lodged in the pulmonary artery."

With this exception, I know of no other recorded case.

The cases of osteomata admitted to Guy's Hospital during the years 1889 to 1901, inclusive, show the following statistics:

Subungual	26
Femur (lower end)	18
„ (upper end)	1
Tibia (upper end)	8
„ (shaft)	1
„ (lower end)	1
Humerus (upper end)	4
„ (lower end)	1
Calvarium	4
Orbit	3
Scapula	2
Fibula (upper end)	1
„ (lower end)	1
Radius (lower end)	1
Metacarpus	1
Auditory meatus	1
Cervical vertebræ	1
Leontiasis ossea	1
Multiple osteomata	6
Total	82

Of the cases of subungual osteoma one was unusual, in that it sprang from the third toe. Of the remainder, among the single cases the following points may be mentioned:—Among the cases occurring at the lower end of the femur, one was fractured by accident, and one caused complete outward dislocation of the patella, while a third was accompanied by a syphilitic ulcer.

The case in which the tumour grew from the shaft of the

[1] 'Tumours, Innocent and Malignant,' chap. iv, p. 42.

[2] 'Virchow's Archiv,' Bd. xxxv, p. 501.

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tibia is noteworthy in that, although arising in this unusual situation, it was capped by cartilage, and was apparently the result of an injury. The mass, which grew from the lower end of the tibia, displaced the fibula to such an extent by pressure that the latter bone was reduced at that point to a mere layer of compact tissue.

In the orbital cases abscess was present twice.

The vertebral case was complicated by gangrene of the third finger from pressure on the subclavian artery, and marked wasting and anæsthesia from pressure on the brachial plexus.

Injury seems to have had but little relation to the formation of these growths, for among the subungual cases a direct history could only be obtained in four, or 15·31 per cent. In the remaining cases the figures are even less striking, seven cases giving as a result 12·5 per cent.

An examination of the family history of all the cases (excluding all doubtful histories) showed only the presence of rickets in two, rheumatism in three, and phthisis in two.

None of these were drawn from the subungual cases.

With regard to the age-frequency, the following is the tabulated result, given in decennial periods:

	1st.	2nd.	3rd.	4th.	5th.	6th.
Subungual cases	1	16	7	2	0	0
Other cases .	8	32	9	5	1	1

Sex.—Here a most marked contrast occurs under both classes, for not only is the frequency reversed in each, but in each the numbers are nearly doubled; thus in the subungual cases the numbers are, males 9 cases, or 34·6 per cent.; but females 17 cases, or 65·38 per cent.; while in the other cases the results are, males 37 cases, or 66·25 per cent.; but females 19 cases, or 33·92 per cent.

Heredity appears to have had but little influence in the cases analysed here, but a point of interest lies in the fact that each of the cases in which any evidence of it was found belongs to the series of multiple osteomata.

Multiple cases.—In the first of these cases the tumours numbered forty; among the more unusually situated of them, one grew from the neck of the astragalus and one from the outer side of the os calcis. This patient, moreover, developed a purpuric rash while in hospital.

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In the third case the tumours numbered over two hundred. There was a bony mass in the substance of the latissimus dorsi muscle, and both patellæ were studded with nodules. In this connection it is noteworthy that I have recently seen a bony outgrowth from the sesamoid bone of the tibialis anticus tendon. On the external malleolus was a large mass which had caused ulceration of the skin by pressure.

The fourth case showed about thirty masses, and of these, two arose from the outer side of the cuboid bone.

The fifth and sixth are of special interest from the fact that both of them developed thoracic tumours, the latter being the case of which I have shown the specimens to-night. In each of these there was evidence of heredity, the father of the former and the son of the latter both having several bony masses about their limbs; in each a tumour formed in the thoracic wall: in the former the tumour grew rapidly and was removed, and although reported to be a simple chondroma, its exceedingly rapid growth and its general appearance were suggestive of early malignancy; in the latter the tumour, originally a simple chondroma, did actually become malignant, and destroyed the patient. It has since come to my knowledge that the mother of the deceased patient herself died some years previously from what was described as a "bleeding cancer of the face," and I have endeavoured to obtain further evidence of its true nature, in view of the possibility of its having been a chondro-sarcoma of the parotid gland. *January 7th*, 1902.

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34. *Congenital multiple sarcomata of the skin.*

By George Pernet.

(From the Clinical Laboratory of University College Hospital.)

In May, 1901, the dead body of a new-born female infant was brought to the Skin Department of University College Hospital by Dr. Jordan Harvey for Dr. Radcliffe-Crocker's opinion with

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regard to numerous tumours which existed in the skin. The conclusion arrived at was that the growths were probably of a sarcomatous nature. A few were removed at the time for further examination, and later on handed to me. No *post-mortem* examination was possible, either then or at any other time, owing to the objection of the parents. And although on this account the case is unfortunately incomplete, the great rarity of the affection of the skin is, I think, a sufficient reason for bringing it before this Society.

The confinement was attended by Dr. Jordan Harvey, of Canning Town, to whom I am indebted for the following excellent notes:—"The father of the child is thirty-one years of age, strong, and healthy. He is one of a family of eleven. Two of his brothers died at eleven and forty respectively, and one sister at thirty; the cause of death unknown. Their mother, aged 76, is living. Their father was killed in an accident at fifty-four. There is no history of syphilis.

"The mother of the child is thirty years of age. She has two sisters who have families, well and healthy. A brother died at sixteen months from bronchitis. Their father is said to have died from 'apoplexy' at thirty-two, and their mother, who is living, is stated to be suffering from 'cancer of the stomach.'

"The couple have been married three years. Their first child is 'delicate in the chest;' their second is the baby in question. Soon after she fell with this child, the mother says she had an attack of 'shrimp-poisoning,' and at about the fourth month of gestation she saw 'a man run over by a tramcar.' She has two or three warts about the face.

"The baby was born naturally at full term on May 5th, 1901, and weighed just under six pounds at the time of her death on May 7th. The placenta was normal. She cried lustily, but did not suck satisfactorily, and looked thin and puny.

"As to the growths, there were in all seventy-one, situated on the face, on the back, and on the flexor aspect of the limbs, in which latter regions they appeared to map out the superficial cutaneous nerve-distribution. There were no growths on the head, chest, and abdomen. The left auditory meatus was occupied by a growth, and at the time of birth a meconium-stained growth protruded from the anus. I at first took it for stained mucus only, but on carefully washing it with

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tepid water I found it was a growth feeling like those in the skin. This, by the third day, had retracted into the rectum. The right eyeball was very prominent, and its tension greatly increased; its sclerotic was very jaundiced, and the pupil very widely dilated. There was no external deformity of the orbit.

"The skin growths, measured across, varied from $\frac{1}{8}$ to $\frac{3}{4}$ of an inch (about 3 mm. to 2 cm.). Some were perceptible only to the touch, while others were quite prominent and from $\frac{1}{4}$ to $\frac{3}{8}$ of an inch (about 6 to 10 mm.) above the level of the skin. In colour they varied from that of the skin (these appeared to be subcutaneous) to a dark purple hue (in which case they appeared to be implanted in the skin). To these purple-coloured growths pressure made no difference.

"The lymphatic glands were enlarged. In the lower third of both thighs and in the substance of the calves were large masses of growth."

Dr. Harvey adds that the left leg appeared to be shorter than the right, and on measuring from anterior superior spine to malleolus a difference of $\frac{1}{4}$ inch was found. The left knee could be dislocated quite easily. The child grew progressively weaker, and died on the third day.

A few of the skin growths were removed *post mortem*, as I have already stated, placed in alcohol, and handed to me. I did not see them in their recent state. I have examined two of these. The larger was more or less pea-shaped, and from $\frac{1}{8}$ to $\frac{1}{4}$ inch (about 5 mm.) in diameter. This was hardened in alcohol and cut in celloidin, and sections were stained in various ways: picro-cochineal, polychrome-methyl-blue and orcein, Van Gieson, Pappenheim (plasma-cell stain), hæmatoxylin-eosin. The last-named gave the best results as far as the cellular structure of the growths is concerned. The growth was made up of closely aggregated cells, more or less of the small round-cell type, but which varied in shape owing to their close juxtaposition. The protoplasmic parts of the cell did not stain well, and could only be well made out with the $\frac{1}{12}$ oil immersion, but to some extent also with $\frac{1}{6}$. These were stained faintly yellow by Van Gieson and faintly pink by hæmatoxylin-eosin, by the latter stain the outline of the cells showing up. The nuclei also varied greatly in shape—round, oval, etc. There were

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irregular mitoses. This growth was distinctly situated in the corium, the papillæ of which were flattened over its convexity, which reached close up to the epidermis. The connective tissue pushed aside by the growth formed a kind of capsule to it, but here and there in the upper parts the sarcoma cells were breaking through in strands into the surrounding corium. A marked feature of the growth was the very great number of vascular clefts, more or less irregular, or oval, or circular. With very few exceptions they did not contain blood. Their endothelial lining could not always be made out. Pappenheim's plasma-cell staining method was negative.

As to the second smaller growth, that was cut in paraffin, and stained by the hæmatoxylin and hæmatoxylin-eosin methods. It differed from the first growth in being more diffuse and flattened, without the encapsulation I have just referred to. Moreover, the sections of the vessels were mainly circular and oval, with few irregular clefts, as compared with the spherical growth previously described. Nor were the epidermis and papillary layer of the corium flattened over it, the epidermal surface being on the contrary rather wrinkled. This growth was evidently in an earlier stage of development.

From the foregoing facts, the case is one of multiple congenital sarcomata of the skin, and the condition may be classed as one of small round-cell angeiosarcoma cutis. Congenital sarcoma of the skin is an exceedingly rare condition. Virchow, in his work on 'Die krankhaften Geschwülste' (1), says that "*Fälle von congenitalem Sarkom sind fast gar nicht bekannt.*" He mentions only two cases, recorded by Mr. Timothy Holmes in the 'Transactions' of this Society (2). Neither of these cases can be compared with the one I have brought before you, as far as the skin is concerned. One was a tumour of the orbit; the other a growth on the back of the neck which, microscopically, according to Dr. J. W. Ogle, Mr. Adams, and Mr. Holmes, was a fibro-plastic growth which had probably originated from the deeper layers of the skin. Dr. Léon Perrin, in his monograph on 'La Sarcomatose Cutanée' (3), gives no instance of multiple congenital sarcomata of the skin. Cristiani, writing on congenital neoplasms (4), mentions that Picot (5) found only eight cases in which the skin was involved primarily out of a total of 242 cases of malignant neoplasms in children; but a reference to

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Picot's paper shows it to be merely statistical and without details. I have consulted a number of other works and papers, and have found only two cases which can be mentioned as having any connection with the subject before us. Dr. John Phillips and Mr. Alban Doran brought before the Obstetrical Society (6) a case of congenital sarcoma in a new-born infant. It was the eighth child. There was no history of malignant disease and no specific taint. At the sixth month of pregnancy the mother had received a blow, which was followed by a cessation of the fœtal movements for two to three days. On the forehead there was a large growth, which bled profusely on the passage of the head. In addition to this there were several smaller growths about the face, which were bluish on the surface. A nodule was found in the right parotid, another between the pleura and intercostal muscles on the right side, and one in the liver. The kidneys showed no changes. The forehead growth was found to be a small round-cell sarcoma which had developed in the subcutaneous tissue. But Mr. Doran, at a subsequent meeting of the Obstetrical Society, stated in the discussion on Dr. Herbert Spencer's "Visceral Hæmorrhages in Still-born Children" (7), that the foregoing growth might have arisen in an extravasation of blood.

The second case is that of Ramdohr's (8). The birth was normal, but the infant died shortly after as a result of hæmorrhage from a tumour on the chin. The family history as to syphilis, tumours, or other disease was negative. There was a large tumour on the chin and lower part of the cheek. There were also about a dozen tumours of the skin, from a lentil to a hazel-nut and more in size. In the left groin region there was one as large as a pigeon's egg. There were also growths in both kidneys, in the lungs, and on the posterior surface of the sternum. The other viscera were normal. The tumours of the kidneys and lungs were poor in vessels, but those of the skin were highly vascular. The case was one of sarcoma (angeiosarcoma).

As to ætiology, this is obscure. In the case I have described it is very possible that the multiple skin growths were secondary. It is unfortunate that no autopsy was permitted, and that the cause of the prominence of the right eyeball could not be investigated. As to the growths about the calves, some por-

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tions were removed, but the specimens, unfortunately, cannot now be found.

I am indebted to Dr. H. Radcliffe-Crocker for allowing me to make use of this case.

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April 29th, 1902.

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35. *Hernia into the processus vaginalis, associated with invagination of the upper part of the sac.*

By RAYMOND JOHNSON.

THE specimen (University College Museum, No. 1621) consists of the parts concerned in an inguinal hernia of the right side. The processus vaginalis is open in its whole length. The part of the process which is distended into a hernial sac has a length of 10 cm., and at its lower and inner part communicates by a rounded opening 1·5 cm. in diameter with the upper end of the distended tunica vaginalis, which has a vertical measurement of 11 cm. The upper part of hernial sac, instead of being directly continued into the parietal peritoneum of the abdominal cavity, is reflected downwards around the whole circumference of its neck to form a secondary sac within the primary sac. The secondary sac measures 5 cm. in length; it is thin and translucent, and presents on both aspects the appearances of normal peritoneum; its lower extremity is widely open, and over the

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edge of it the outer peritoneal layer is continued into the inner layer, which can be traced upwards into the parietal peritoneum. From the abdominal cavity a coil of small intestine passes into the secondary sac and projects through its open lower extremity into the cavity of the primary sac. The inguinal canal has been converted into a direct opening by the approximation of its two extremities. The secondary sac, it is believed, has resulted from complete invagination of the inguinal portion of the processus vaginalis downwards into the part below, this invagination having been rendered possible by the approximation of the two extremities of the inguinal canal. It is probable also that the tendency to invagination may have further been increased by the existence of a narrowing at the upper end of the processus vaginalis at its opening into the peritoneal cavity.

The specimen is of some interest in connection with the much debated subject of "encysted hernia." The researches of Lockwood ('Med.-Chir. Trans.,' vol. lxix, 1886, p. 479) showed that when a hernial sac projects into the cavity of the tunica vaginalis the relation of the hernial sac to the tunica is essentially the same as that of the so-called "infantile hernia." In its usual form the latter is characterised by the presence of a sac *behind* the upper part of the tunica vaginalis, but in certain cases the hernial sac bulges so much forwards *into* the tunica vaginalis as to appear *encysted* within it. This explanation is supported on many grounds by Lockwood, and the older view, for many reasons, rejected. The older view was to the effect that the upper part of the processus vaginalis was occluded by a fibrous septum or adhesion, and that, by a subsequent distension of this, a hernial sac was formed, which protruded downwards into the tunica vaginalis, and became "encysted" within it.

The specimen under consideration differs from an encysted hernia in that the lower extremity of the sac, which hangs into the tunica vaginalis, is open and not closed. This is a necessary result of the fact that the upper end of the processus vaginalis was in open communication with the peritoneum, and thus, after the gradual prolapse or intussusception of the upper part of the process, the original open upper end of the latter has come to form the open lower end of the dependent sac.

It seems, however, not improbable that, had the upper end of

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FIG. 26.

The figure shows the patent processus vaginalis, dilated above into a hernial sac; a probe has been passed along the process between the tunica vaginalis and the sac. Into the hernial sac there projects a second sac, which is unclosed below, and through the open lower end of which a coil of intestine (in the reduced figure about an inch in length) protrudes. From a drawing by Mr. T. W. P. Lawrence.

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the processus vaginalis been closed (not by a septum, but by actual obliteration of the lumen), the same process of prolapse or intussusception would have produced a complete sac instead of one open inferiorly—in fact, an encysted hernia. Lockwood, in the paper quoted, says, "I do not think it has ever been argued seriously that an encysted hernia would be produced by an intussusception of one part into another, for, owing to the gradual nature of the constrictions, this would seem to be an impossibility." This specimen weakens the force of this argument; for if, as seems clearly the case, intussusception can occur in an open peritoneal tube, surely it might still more readily occur in a peritoneal tube which is at one spot obliterated.

Finally, reference may be made to an article by Jaboulay ('Traité de Chirurgie,' Le Dentu and Delbet, 1899, vol. vii, p. 684), in which diagrams are given illustrating invagination of the upper part of the processus vaginalis into the tunica vaginalis below, the upper end of the processus being in the one case open and in the other case closed.

February 18th, 1902.

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36. *Hæmorrhage into adrenals—an intestinal toxæmia.*

By Clive Riviere.

I am showing to-night the organs from four cases of supra-renal hæmorrhage, which occurred at the East London Children's Hospital, Shadwell, in the spring of last year.

Circumscribed hæmorrhage into the substance of one or both supra-renal bodies is not a very uncommon condition, and occurs usually in the new-born, or within the first few days of life; but the specimens I am bringing before you to-night show a condition entirely different from this, and one of which only a few examples have been recorded. Instead of a blood-cyst being formed, there is a general infiltration of the tissue with blood-cells, giving the appearance of hæmorrhagic infarction; and the pathological conditions are accompanied by a no less distinctive train of symptoms.

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Similar cases have been described and the organs exhibited before this Society in the year 1898—one case by Dr. Andrewes, one by Drs. Garrod and Drysdale, one by Dr. Still, and one by Dr. Frederick Batten. In addition to these four cases there are two more, both of which occurred at St. Bartholomew's Hospital, and were described by Dr. Eustace Talbot in the hospital reports for the year 1900. These, with the four cases I am exhibiting to-night, make altogether ten recorded cases of this disease. There are, it is true, two cases with apparently similar pathological appearances recorded by Mattei, one a fœtus and the other an infant dying on the second day, but in these the symptomatology appears to have been different. Thus the condition is rare, and, seemingly, has only appeared among us of recent years; and yet the clinical and pathological peculiarities of the condition are so striking that it constitutes nothing less than a new disease, and one which can readily be diagnosed. I had the good fortune to witness the *post-mortem* examinations on two of the cases occurring at St. Bartholomew's Hospital, and was thus enabled to correctly predict the lesions found after death in the first of the Shadwell Hospital cases from the appearance of the body and the description of the clinical symptoms. The other three cases were readily diagnosed during life by the house physician.

As the full notes of these cases were published in the 'British Medical Journal' for July 13th of last year, I will not trouble you with them here, but will give a short *résumé* of the clinical symptoms.

Clinical symptoms.—A healthy, well-nourished child in the latter half of the first year of life goes to bed in normal health. In the night it wakes up and vomits, thereafter is restless, and again vomits some hours later. Later still diarrhœa may set in. The temperature rises to 101° or 102°, petechiæ appear on the skin, and often therewith some purplish mottling. If a hypodermic injection is given a black bruise is left. The temperature soon rises higher, to 104° or so, and there may be hyperpyrexia. Convulsions occur in some cases, in others not. Nothing is found on examination, the abdomen is quite normal; there are generally râles in the lungs. The child becomes collapsed, restless, and anxious, with dusky countenance, cold extremities, feeble, rapid pulse, and shallow respirations, and dies in

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from twelve to forty-eight hours after the first onset of symptoms.

Post-mortem examination.—At the *post-mortem* examination, besides ecchymoses and petechiæ scattered over the body, there is generally a purplish mottling which may be apparent during life, but increases markedly after death.

The organs generally are much engorged, and a few pin-point hæmorrhages may be found. The lungs show areas of very dark, engorged collapse. The spleen is not unduly large.

Besides the appearance of the supra-renal glands, the most noticeable condition present in these four cases was that of the Peyer's patches and the mesenteric glands. The former were in all cases markedly swollen and prominent, as in an early stage of enteric fever, but showed no loss of surface. The solitary follicles, on the other hand, were not affected. The mesenteric glands were noticeably enlarged.

The supra-renal capsules were larger than normal, dark mahogany-red on the surface and on section, the medulla being generally darker than the cortex. In one case certain areas of the gland kept their normal appearance; in another case, as in that described by Dr. Still, only one supra-renal was hæmorrhagic, the other being only somewhat congested. No venous thrombosis was present.

Bacteriology.—In two of the cases cultures were taken from the heart's blood and spleen; in one of these many different culture media were used, both aërobically and anaërobically, but all remained sterile; in the other case an agar culture from the spleen grew a bacillus which appeared to be a variety of *Bacillus coli communis*. Sections of the supra-renals stained with Czinzinsky's solution failed to show any micro-organisms.

Histology.—The supra-renal capsules examined microscopically show a general infiltration of the tissue with blood, most marked in the medulla. In the slighter cases the cells are not destroyed, but in those more advanced the cellular elements appear much diminished in number and are represented by only shrunken and distorted nuclei, the cell protoplasm having disappeared. In the least advanced case islands of unaltered cells are left surrounding the central veins.

Conclusions.—We have, then, an acute disease beginning insidiously, but working up rapidly through a definite group of

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symptoms to a fatal termination. Out of the ten recorded cases it is remarkable that seven were unvaccinated, while of the remaining three, in two it was not noted, and in only one case had vaccination certainly been performed, two good marks being present. On the other hand, no source of variolal infection was found, no cases occurred subsequently in the families of those attacked, nor was variola at that time epidemic. In the recent epidemic, moreover, no similar cases have been recorded.

The cases bear a striking resemblance to cases of poisoning from decomposing food, and also in many ways suggest a bacterial toxæmia, such as we may presume to occur in the epidemic diarrhœa of infants. In either case the vomiting and diarrhœa, and swelling of the Peyer's patches and mesenteric glands, point clearly to the alimentary canal as the seat of toxic absorption.

With regard to poisoning with bodies already formed in food products, though the disease rapidly reached a fatal termination in each case, yet the onset and early symptoms seem to me too insidious to admit of this explanation. Some, indeed, of the recorded cases, examined in an early stage, were allowed to leave the hospital, as the condition did not then appear serious. Again, on inquiring into the feeding of the four Shadwell cases no suspicious article of food taken by all could be discovered. One, indeed, had eaten sausage on the day previous to the attack, but the other three had not. The insidious and gradually increasing severity of the symptoms is much more easily explained on the assumption of a bacterial invasion of the intestinal tract with the gradual formation and absorption of toxins leading to the symptoms and pathological changes observed. In view of the negative cultural and microscopic results in most of the recorded cases, it is unlikely that there was a septicæmic condition present. It has been shown that in animals congestion of the supra-renals may be caused by inoculation with various pathogenic organisms, such as *Bacillus diphtheriæ*, *Bacillus pyocyaneus*, and Friedländer's bacillus, and in the case of the first two organisms the injection of their toxins alone led to a similar result. Thus the condition forming the most striking feature of the cases under discussion may be caused in animals by any one of several organisms, and this should make us cautious in suspecting a specific cause for this

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disease, especially since in man the organisms of many of the specific fevers may lead to hæmorrhagic conditions if sufficiently virulent or introduced in sufficient numbers.

In view of the possibility of a specific pathogenic organism being the cause of these cases in infants, it is interesting that three of the Shadwell cases occurred within an interval of twenty-three days, and yet the localities of their habitation were so widely separate as to make a common source of infection almost inconceivable. *May 20th*, 1902.

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37. *The bone-marrow in a case of suppuration of the knee-joint with secondary hæmorrhage.*

By Arthur G. Phear.

[With Plate XI.]

Since Ehrlich formulated his theory that the bone-marrow is the source of the polymorphonuclear blood-corpuscles, and therefore the tissue chiefly concerned in the polymorphonuclear leucocytosis which accompanies most acute infective diseases, it has become a matter of great interest to investigate the state of this tissue in cases of infective disease whenever opportunity may arise.

Ehrlich based his views as to this function of the bone-marrow on grounds that are mainly histological (1). He drew attention to the similarity of the protoplasm of the polymorphonuclear blood-cells to the protoplasm of certain of the marrow-cells, laying special stress on the size and colour-reaction of the contained granules. He found in the bone-marrow cells that he regarded as illustrating stages in the development of the myelocyte with its simple rounded nucleus into the polymorphonuclear blood-cell with its complex contorted nucleus. He also sought to show that in diseases involving the replacement of the bone-marrow by some indifferent tissue, as in acute leukæmia, there is a diminished output of the polymorphonuclear cells, as may be inferred from the reduced number of these cells in the blood.

More recently the subject has been approached from the experimental standpoint by Roger and Josué, with very inter-

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esting results (2). These observers inoculated adult rabbits subcutaneously with staphylococcus of moderate virulence. After forty-eight hours there was local suppuration, and the number of leucocytes per cm. of blood was increased from twelve or fifteen thousand to thirty or forty thousand. In animals killed at this early stage there were already changes in the bone-marrow, but these became much more marked if the animal was allowed to live until the fifth day, by which time they found that the character of the marrow was completely altered. The fat, of which the normal tissue is chiefly composed, had disappeared, and was replaced by a cellular tissue. The predominating cells were myelocytes, with a fine granulation of so-called neutrophile reaction. Among the cells were forms of an intermediate character between the mononuclear granular cells and the polymorphonuclear white corpuscles. They found also a relatively slight increase of cells containing eosinophile granules, and of nucleated red blood-corpuscles. Giant-cells were present in abundance; karyokinetic figures were scanty. They concluded that the bone-marrow undergoes a special reaction in staphylococcus infection, the essential change consisting of a proliferation of the finely granular cells with rounded nuclei, which they consider, with Ehrlich, to be the parent-cells of the polymorphonuclear blood-corpuscles.

Their work has been in great measure confirmed by the researches of Muir (3). Experimenting on rabbits, he employed injections, subcutaneous and intra-peritoneal, of *Staphylococcus pyogenes aureus*, and in one observation of an attenuated culture of pneumococci from a case of ulcerative endocarditis. He found that the resulting leucocytosis was associated with changes in the marrow of a double order: (1) passive or degenerative changes, in the giant-cells especially, more rarely in the myelocytes; (2) active or formative changes, affecting chiefly the finely granular myelocytes, which were greatly increased in number and showed evidence of division by karyokinesis. He regarded the proliferated marrow tissue as directly concerned in the production of the polymorphonuclear leucocytosis.

Pathological observations up to the present tend to show that in the human subject infective disorders are accompanied by

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changes in the marrow structure, and that the changes bear a close analogy to those which may be induced in animals by experimental infection. A general account of the marrow "reactions" in infective diseases was given by Muir in a recent communication to this Society. The object of the present paper is to record the state of the marrow, hitherto, so far as I know, undescribed, in a case of combined suppuration and secondary hæmorrhage.

A man aged 35 was admitted to the Royal Free Hospital on October 27th, 1901, suffering from a crush of the right arm, fracture of the right femur, and dislocation of the left knee, the results of a train accident. The arm was amputated, the thigh fixed on a splint, and the dislocation reduced. The stump of the arm healed by first intention, and the fractured femur in due course became united. The left knee-joint, however, suppurated. There was a patch of badly bruised skin on the external aspect of the damaged joint, and the underlying tissues subsequently became necrosed, and it was presumably by this path that infective organisms gained access to the joint-cavity. On November 14th the knee-joint was opened and the pus evacuated. Tubes were introduced, and the joint was irrigated daily, but suppuration, nevertheless, continued freely until November 25th, when there was a profuse hæmorrhage from the joint, the patient losing approximately a pint of blood. He was urged to have the popliteal artery tied, but refused. Two days later there was a second attack of hæmorrhage, the amount lost being about the same as before. The popliteal artery was then tied, and normal saline solution was injected into the vein. The patient, however, did not rally, and death took place a few hours later.

At the autopsy the marrow occupying the upper part of the shaft of the femur was found to be opaque, of a pale red colour, and firm in consistence. The tissue was hardened for four days in absolute alcohol; sections were cut and stained for a few minutes in dilute hæmatoxylin, and then for two hours in Ehrlich's tri-acid stain.

On examining with a low power it is seen at a glance that the marrow has undergone great modification. The fatty tissue which normally occupies the shaft of the femur is largely replaced by a cellular tissue. The change has advanced to a

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greater extent in some parts than in others, and by comparing different parts it can be made out that the fat areas are gradually encroached on and circumscribed by a proliferation of the cells which, in small numbers, normally occupy the septa and angles between adjacent fat-spaces. In the more advanced stages the septa are so much increased in thickness and the fat-cells are so much contracted that the bulk of the tissue is composed of the newly formed cellular structure. With a higher magnification three orders of cells can be distinguished. These are—(1) cells belong to the myelocyte group with large rounded nucleus and granular protoplasm; (2) cells belonging to the group of erythroblasts, characterised by the dense opaque staining of their nuclei in solutions of hæmatoxylin; (3) giant-cells.

The *myelocytes* form the predominant group. They are large rounded cells, with a diameter of 10 to 12 μ. Each cell contains a single nucleus, round or oval, and rather bulky, its diameter being rarely less than half that of the whole cell. The nucleus is poor in chromatin, and stains comparatively feebly. The protoplasm has a granular appearance, though it is not granular in the strict sense that discrete granules can be individually distinguished, even with the highest powers. A diffuse pink tinge is imparted to it by the acid-fuchsin constituent of the tri-acid stain. Deviations from the above type may be observed; for example, (*a*) cells containing two rounded nuclei, apparently separate from one another; (*b*) cells consisting of little else but a well-formed nucleus; (*c*) cells with protoplasm containing coarse, refractile granules, recognisable as discrete bodies, and staining deeply with acid-fuchsin; (*d*) cells whose nuclei are not rounded, but variously modified, some with a deep indentation, others reniform, and others elongated and bent upon themselves. The last-mentioned cells occur in groups, and they are of special interest, since the characters of their nuclei suggest that they may be transition forms in the course of development into adult polymorphonuclear blood-corpuscles. Search was made, extending over many sections, for karyokinetic figures, but with a negative result.

Erythroblasts, though less numerous than the myelocytes, are nevertheless abundant, and may be at once distinguished by their nuclei, which, with hæmatoxylin, become uniformly and

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opaquely stained a deep blue or blue-black colour. No trace of nuclear network can be seen. The nucleus is round, and, for the greater number of cells, remarkably constant in size, hardly varying in either direction from an average diameter of 4 μ. The difference in the size of individual cells depends almost entirely on the varying thickness of the perinuclear protoplasm. In the larger number the scanty protoplasm forms but a thin covering for the nucleus, free from granules, and staining a clear red colour with acid-fuchsin. Occasionally no protoplasm at all is visible, and the whole cell is apparently composed of nucleus. Other cells possess an abundance of deeply staining protoplasm. The larger cells are usually solitary; the smaller ones are generally arranged in groups of three to ten individuals in close contact; sometimes there appears to be common protoplasm around two or three nuclei. No karyokinetic figures were found.

The presence of so many erythroblasts is a matter of interest in connection with the considerable hæmorrhage that occurred two days before death; it may be regarded as a sign that a compensatory erythroblastic reaction was in full progress when the second attack of hæmorrhage, involving a rapid and fatal loss of strength, supervened. If the thickness of the protoplasmic rim may be taken as an index of age, by far the larger number of these cells had arrived at a similar stage of growth.

Giant-cells, of which there are said to be none in the femur under normal circumstances (4), are present in abundance. They are remarkable for their size, their irregular shape, and the complexity of their nuclei. The measure of the greater diameter, exclusive of processes, which may attain great length, is seldom less than, and often considerably exceeds, 20 μ. One of the figured cells is 24 μ by 33 μ. The thickness is such that a single cell can often be traced through four or five sections arranged in serial order. The protoplasm is somewhat granular, and gives a diffuse colour reaction with the tri-acid stain nearly, though not quite, as intense as that of the protoplasm of the erythroblasts. The nucleus exhibits great irregularity in structure, but it is generally possible to trace continuity between its parts, especially if the examination be extended to a series of three or more sections. The function of the giant-cells is unknown.

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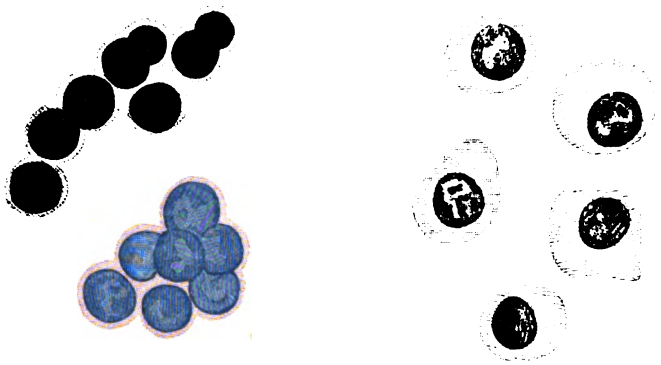
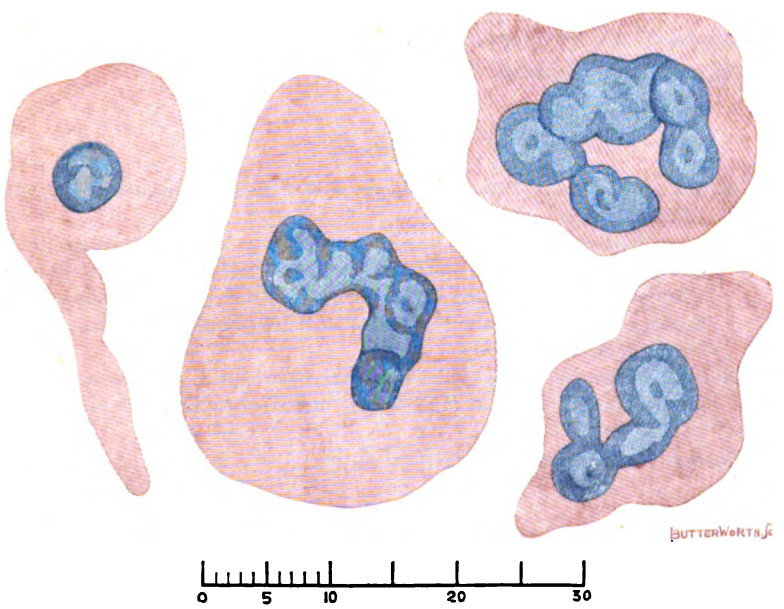
Fig. 27.



The figure shows on the left-hand side two groups of young erythroblasts from the bone-marrow; nuclei of almost uniform diameter, deeply stained; protoplasm scanty. On the right-hand side are five large erythroblasts with abundant clear protoplasm, deeply coloured with the "acid" constituents of the stain. Hæmatoxylin and Ehrlich's tri-acid stain. (Drawn with the camera lucida.)

Fig. 28.



Showing some of the giant-cells from the bone-marrow. The largest, as seen by the scale below, measures 24 μ × 33 μ. The continuity of the different parts of the complex nucleus has been traced by superimposing drawings made at different focal planes. Hæmatoxylin and Ehrlich's tri-acid stain. (Drawn with the camera lucida.

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The interest of the marrow changes in this case depends on the indication which they afford that at the time of death a twofold reaction was in progress, the one part of a defensive character and related to the infection with pyogenic organisms; the other part reparative, to make good the loss of the red blood-corpuscles. The structural feature common to both forms of reaction is the disappearance of the fatty parts of the marrow and their replacement by a tissue rich in protoplasmic cells. Every kind of the ordinary marrow-cells contributes to this new tissue, but in unequal degree. It has been shown by Muir and others that in the reaction usually accompanying infection the stress of active growth falls on the myelocytes and allied cells, the parent-cells, as it is supposed, of the polymorphonuclear blood-corpuscles. In the reaction to hæmorrhage, on the other hand, it is well known that the cells chiefly involved are the erythroblasts, which are generally recognised as the parent-cells of the red blood-corpuscles. In the case under consideration there was the double factor of suppuration and hæmorrhage, and in the state of the marrow there is to be found evidence of a corresponding activity on the part of both myelocytes and erythroblasts.

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June 17th, 1902.

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DESCRIPTION OF PLATE XI,

Illustrating Dr. A. G. Phear's communication on the Bone-marrow in a Case of Suppuration of the Knee-joint with Secondary Hæmorrhage. (Page 372.)

From photographs of sections of medulla removed from the shaft of the femur.

Fig. 1.—An early stage of proliferation of the cells lying in the septa and angles between adjacent fat spaces.

Fig. 2.—An advanced stage, showing considerable overgrowth of cells, encroaching on and in some places obliterating the fat areas.

Fig. 3.—Higher magnification of the cellular tissue. The cells shown here are chiefly myelocytes, with granular protoplasm and round or oval nuclei. The nuclear network is well seen.

Fig. 4.—The cells in this part of the tissue are chiefly young erythroblasts, with deeply-stained, almost black nuclei, and scanty protoplasm.

Fig. 5.—Shows one large giant-cell and two or three smaller ones. In the upper part of the figure are cells with irregular lobulated nuclei, probably transition forms between the myelocyte and the polymorphonuclear leucocyte.

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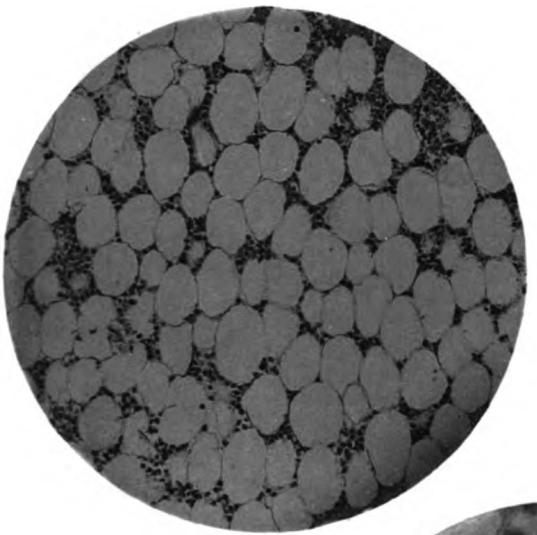

Fig. 1.

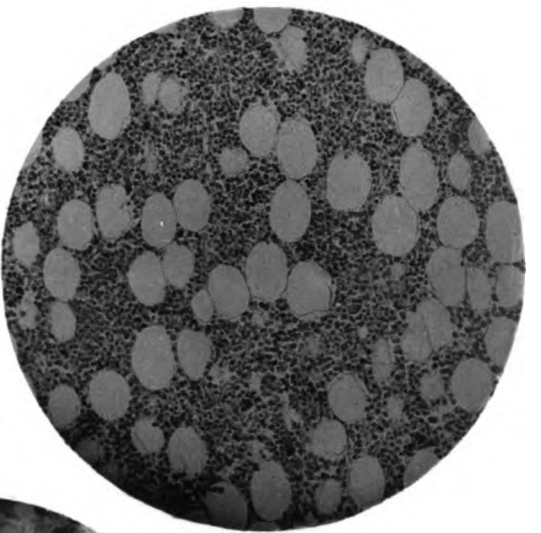

Fig. 2.

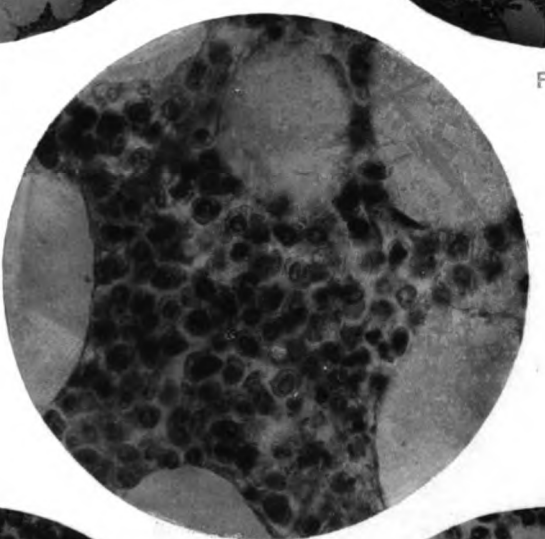

Fig. 3.

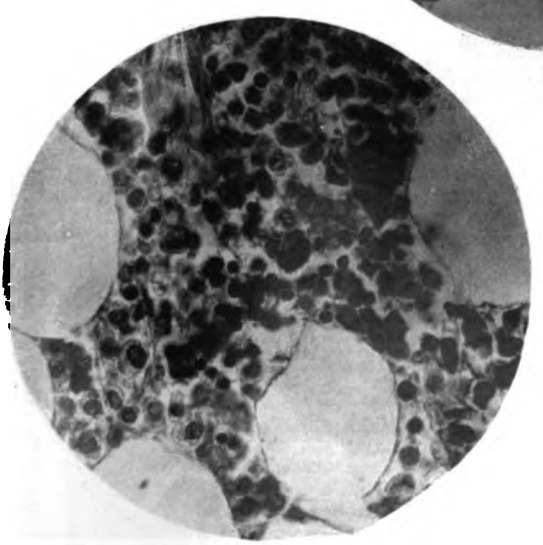

Fig. 4.

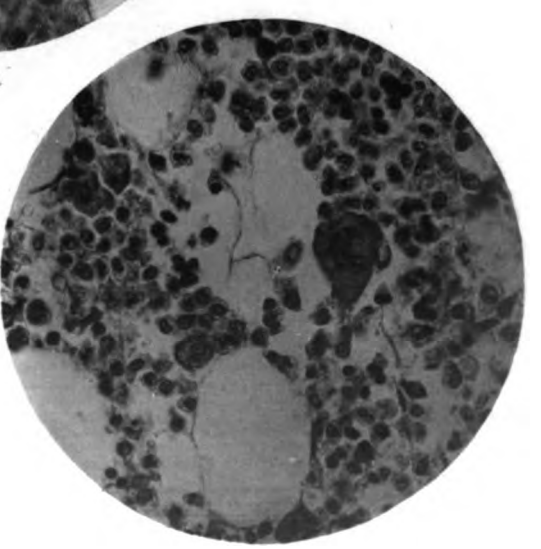

Fig. 5.

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38. *The reactions of the bone-marrow and other leucocyte-forming tissues in infections.*

By Robert Muir (Glasgow).

[With Plates XII, XIII.]

As the result of numerous researches on the behaviour of the cells of the body in infective conditions, the importance of the leucocytes has been abundantly demonstrated, both as regards intra-cellular digestion and as regards the source of bactericidal and other antagonistic substances. The increase in number of those cells under abnormal conditions is thus a phenomenon well worthy of consideration, not merely as a histological change, but as constituting the underlying basis for the increase of the defensive powers. Furthermore, the behaviour of the different forms of leucocytes in diseased states guides us in judging as to the significance of the different morphological characters of the cells in question. We may also assume with safety that there must be some simple fundamental laws or principles governing the multitudinous leucocyte variations which have been observed in the blood in different diseases; and it is apparent that in order to arrive at such principles we must compare the changes in the leucocyte-forming tissues, and in the tissues generally, with those present in the blood. These are some of the considerations which guide us in the study of the subject.

It would be quite out of place to describe the different varieties of leucocytes, their distribution in the tissues, etc., but some preliminary reference may be made to the chief sites of leucocyte activity. It is well recognised that cell multiplication and functional activity are vital processes differing in kind, and that there are often to be observed corresponding histological characters. This is well exemplified in the case of the finely granular leucocytes, and in a corresponding manner, it is to be noted, the proliferative processes are more active in some places, the phenomena of phagocytosis in others. In the Mammalia the multiplication of leucocytes takes place chiefly in definite areas in special relation to the blood and lymph-streams respectively, these being strikingly adapted to the needs of the

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economy. Apart from these special positions, leucocyte proliferation, with exceptions in pathological conditions afterwards to be mentioned, is comparatively rare. The bone-marrow is *par excellence* the seat of the multiplication of the granular cells, neutrophile and eosinophile, and, as I have elsewhere pointed out, the vascular arrangements are such that an enormous number of these cells can be thrown into the circulation in a short time. It has been called by Ehrlich a defensive tissue, "Schutzorgan," but it must be understood that this term is to be used in reference to the cells supplied by it, and not as indicating that it is a special site of phagocytosis. As a matter of fact, phagocytosis in the bone-marrow is relatively a secondary matter, and in this respect a contrast may be drawn with the splenic pulp. I am not aware that the lymphatic system in the marrow has ever been fully worked out, but I think we may hazard the statement that its cells have no special relation to the lymph-stream, and that they do not leave by the lymphatics. Myeloid tissue is thus essentially a formative tissue; it is structurally arranged for the supply to the blood of its characteristic elements—red corpuscles and granular leucocytes.

In speaking of lymphoid tissue, we may restrict the term to the tissue in whose germ-centres lymphocytes are produced—the follicular tissue of lymphatic glands, solitary glands, Malpighian bodies of spleen, etc., may be taken as a type. It is essentially a formative tissue, and phagocytosis takes place in it only in certain restricted conditions. It differs from myeloid tissue not only as regards the cells which are formed in it, but also as regards its vascular arrangements. Its capillaries appear chiefly to subserve nutrition, and there is no arrangement by which its cells may readily enter the blood-stream; in fact, it is probable that they do not leave the follicles by this path. The lymph follicular tissue is, however, surrounded by the sinuses and other lymph-paths, and the Malpighian bodies are correspondingly related to the pulp of the spleen. The splenic pulp has, moreover, practically the same relations to the blood-stream as the lymph-sinuses have to the lymph-stream, and we find that a close analogy can be drawn between the two structures so far as pathological processes are concerned. Both are specially constructed for the detention of abnormal elements; in both phagocytosis is of the most active kind, not only bacteria, but also red

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corpuscles and leucocytes being thus destroyed; and in both the cells concerned are closely similar. I cannot state definitely whether or not leucocytes normally multiply in these situations, but in the case of the lymph-sinuses, mitotic division, if it occurs at all, must be very rare, and I consider that the spleen-pulp may be practically excluded as a producer of leucocytes. Under pathological conditions, however, active mitotic division may be observed in both situations, and in this way an abundant supply of non-granular phagocytes is produced. Such proliferation in the lymph-paths and in the splenic pulp is the result chiefly of local disturbances, and is comparable with that seen in various connective-tissue spaces, serous sacs, etc.

In a former paper I gave an account of the changes in the marrow of the rabbit in suppurative and inflammatory conditions, and in the present I shall state the results of a similar investigation in the case of the human subject. I shall also consider the subject of leucocyte reaction in general, and shall compare and contrast the function of the marrow with the spleen and lymphatic glands. I shall state here merely the results of my own observations, and shall not attempt a historical survey of the subject, though incidental reference to the work of others will be made. I have elsewhere given an account of the chief historical facts with regard to the leucoblastic changes in the marrow. A list of some of the more recent papers on the subject, which I have made use of, is appended.

Methods.—The examination of the marrow in the human subject is attended with certain difficulties. In the first place, the examination of the red marrow *in situ* in the spongy bone by means of sections requires decalcification, and this process destroys some of the finer histological characters. There is also the fact that reaction may be shown by extension of the red into the fatty marrow as well as by change in the red marrow normally present. I have taken the marrow of a rib as affording the most reliable standard of comparison, as in newly formed red marrow the cells occur in different proportions according to the stage of the reaction, and differences in character may be noted between the newly formed and the pre-existing marrow. I have, however, carried out an examination of the marrow of the femur in a large proportion of cases. Examination of the marrow has been made (*a*) in film preparations, (*b*) in sections.

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For the former the wet method was used in every case, the fixative being formol-alcohol; in many cases, also, dried films were employed. In only a few cases was the rib-marrow examined *in situ* after decalcification; but a useful method, carried out in the majority of cases, is to express the marrow from the rib and allow the drop to fall into the fixing solution. Thereafter the marrow can be embedded and cut in paraffin. In such cases the structural arrangements are, of course, disturbed, but the relative proportion of fat-cells, myelocytes, blood, etc., can be readily obtained. In the case of the femur, a portion of the marrow sufficiently free from bone-spicules for purposes of cutting can easily be obtained. The part selected should be the upper portion of the shaft, as the change first appears in this situation. The spleen and lymphatic glands were fixed by the usual methods and cut in paraffin. Various staining combinations were employed, but that which gives the best differentiation of the cells is Ehrlich's tri-acid mixture after formol-alcohol fixation.

1. *The bone-marrow.*

I have carried out a careful examination in upwards of seventy cases, the greater number of which have been suppurative or inflammatory conditions,—that is, to speak generally, cases with neutrophile leucocytosis. In addition to the marrow obtained *post mortem*, I have also availed myself of portions of ribs resected for empyema, the advantage being that the cells can be fixed in a perfectly fresh condition. I may say that I have used as controls the marrow from several cases of sudden death as the result of accident. In each case the condition of each variety of cell was noted in the film preparations. A similar procedure was carried out in the sections and the results compared. The film preparations usually give quite satisfactory information on all the important points with the exception of the proportion of fat-cells and the number and condition of the giant-cells.

I shall not give details of the various cases, though these were recorded, but shall enumerate the chief facts obtained.

The marrow in empyema, obtained during life.—This was examined in seven cases of empyema. In six of these the disease was comparatively recent, in one it had existed for a

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long period of time. The ages of the patients varied from seven to sixty. I may state that the changes found corresponded with those obtained experimentally, the essential feature being the increase of neutrophile myelocytes with active mitosis,[1] the fat being relatively diminished, in some cases almost absent. The granules of the neutrophile cells usually appear more distinct than in the normal state. Polymorphonuclear leucocytes of ordinary character are always present, but vary in number; in one case they were numerous, in four cases in fair numbers, and in one they were few, these terms being, of course, used relatively. The eosinophile cells, both myelocytes and their polymorphonuclear derivatives, occur in somewhat varying proportions. They were never, however, increased relatively to the neutrophiles, although there was usually an absolute increase, and in two cases this was distinct. It may be noted that in these marrows the nuclei of the eosinophiles correspond in type with those of the neutrophile series, though the nuclear chromatin of the eosinophile myelocytes is less abundant, and the nucleus of the eosinophile leucocytes is not so much broken up as in the case of neutrophiles. The spherical and deeply staining nucleus so common in the eosinophile myelocyte *post mortem* is practically absent from the fresh marrow. The giant-cells tend to be somewhat larger and even more numerous than in the normal marrow; they occur in the two well-recognised types, that in which the chromatin is abundant and closely arranged, and that in which the nucleus is larger and the chromatin presents a well-marked reticulum; no evidence of active division was seen. The erythroblasts do not appear increased in number, and the proportion of the red blood-corpuscles was relatively low. Evidence of phagocytic action was practically absent. It may thus be stated that there is increase of the cellular marrow as a whole at the expense of the fat, but the outstanding change is the increase in the proportion of the neutrophile myelocytes, with evidence of marked proliferative activity in these cells. The term "neutrophile reaction" will be used as indicating this change, and does not necessarily imply that there is no absolute increase of any form of cell beyond that possessing neutrophile granules. Cases of empyema illustrate the rapidity and extent of the supply of neutrophile leucocytes. By counting

[1] Pl. XIII, fig. 1.

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the number per c.mm. in the pus and noting the quantity of pus the number relative to the number in the blood may be obtained. In one case, for example, I found that the number of these cells in the pleural cavity exceeded twenty-five times the total number in the blood, and this amount had apparently been produced within from two to three weeks.

In the very chronic case pus had been present for a long time, possibly for a year or two, and the pleura was calcified. Here it was evident that the increased supply of leucocytes had ceased some time before, and it was interesting to find that there had been apparently a retrocession in the cellular marrow, the fat-cells being almost as numerous as in the normal condition. One interesting change is that the number of eosinophile myelocytes was very great,—in fact, greater than in any other case that I have observed. This may possibly represent a change corresponding to post-inflammatory eosinophilia.

Other suppurative conditions.—I have examined the marrow obtained *post mortem* in a great many suppurative conditions, of which I may mention osteomyelitis, pyæmia, post-pharyngeal abscess, abscess in neck with gangrene, pelvic suppuration, suppurative peritonitis, etc.; in this group may be placed, so far as the leucocyte changes are concerned, a case of plague. In all such conditions I have found the leucoblastic condition (neutrophile reaction) well marked, though varying in degree. In a case of meningitis due to the *Diplococcus intracellularis* it was very slight; so also in a case of lymphadenoma. In addition to the increase of the myelocytes in the marrow normally red, there is a growth of red marrow in the long bones, to be described presently. In extensive suppuration of long standing the marrow of the femur may be in great part transformed. It is also to be noted that when emaciation is a marked feature the gelatinous condition (*vide infra*) often becomes associated with the leucoblastic conditions (Pl. XII, fig. 6).

Microscopic examination gives corresponding results to those enumerated above, but the following minor points may be noted. In the marrows obtained *post mortem* the proportion of polymorphonuclear leucocytes is much smaller than in the marrow obtained during life; in fact, it may be sometimes difficult to find any. This, I believe, is due to these cells leaving the marrow immediately before death. In the eosinophile myelo-

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cytes the nuclear chromatin is often condensed into a small deeply staining sphere, and in the majority of the giant-cells the chromatin usually has the condensed arrangement, and is sometimes fragmented into irregular masses (*cf.* p. 383). These changes probably represent a degenerative change occurring, or at least commencing, immediately *ante mortem*.

Extension of the red marrow.—The following are the changes observed, for example, in the femur, in the extending marrow at different stages. If one examines the extreme limit of the red marrow, two changes are found proceeding side by side, namely, a marked dilatation of the capillaries, and secondly, an accumulation of the cells around them.[1] Sometimes one of these changes appears to occur first, sometimes the other. On making film preparations of the marrow from such a site, I have found that nearly all the cells are neutrophile myelocytes—only here and there is a non-granular cell present,—and I have obtained no evidence that the cells are first of all non-granular in character and afterwards acquire granules. The two changes mentioned advance side by side, and a little later eosinophile myelocytes are seen to occur singly amongst the groups of neutrophiles. I have failed to satisfy myself regarding the manner in which they appear. Of the non-granular cells, which are probably present from the earliest stage, some undergo enlargement and form giant-cells. Multiple mitosis occurs in such cells in the process of formation, but I have not been able to determine that this results in a brood of small non-granular cells. In one small giant-cell I have found a tetraster, a condition which is not seen in the fully formed giant-cell, and which suggests that the multiple mitosis may in some cases be related to the growth and change in character of the nucleus.[2] At first no nucleated red corpuscles can be seen in the vascular channels, but in course of time they appear and form small lines or groups at the margin of the blood-stream. In this case, also, I am unable to state their source. The later changes are of a progressive nature along the same lines, the fat gradually diminishing.[3] It will thus be seen that in the extension of the marrow all its cells are concerned,—that is, we have not simply multiplication of neutrophiles; what gives the marrow its special character

[1] Pl. XII, fig. 3. [2] Pl. XIII, fig. 3. [3] Pl. XII, figs. 4, 5.

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is merely the relative proportion of the latter.[1] I may also state that after long-continued hæmorrhage, and in pernicious anæmia, the new marrow is formed in the same way, all the elements normally present taking part; here, however, the chief activity is on the part of the erythroblasts.

The marrow in acute pneumonia.—Cases of this disease are of interest on account of its comparatively rapid nature, and in view of the fact that we may, in many of them, assume a comparatively healthy condition before the onset of the disease. Viewed in this light, the changes are of a very striking character. In all, twenty-two cases were examined, the ages of the patients varying from twenty-seven to seventy. In the great majority death had occurred before the tenth day. In all cases the neutrophile reaction was well marked. It may be said to vary according to the age of the patient, being less marked in later years, according to the duration of the disease, and possibly also according to unknown factors, resisting power, etc. Even in old age the change may be extensive. This was the case, for example, in a man aged 70 who died from unresolved pneumonia lasting four weeks. As an example of the extent of the change, we may take the case of an adult with extensive grey hepatisation dying about the seventh or eighth day. The marrow of the rib is usually somewhat pale and lumpy in character; occasionally, however, it may be reddish and may be soft, owing to the large amount of blood present. The diminution of the fat may be extreme, only a few single cells occurring through the section.[2] The neutrophile reaction is extremely well-marked, and mitotic division is sometimes very abundant. Polymorphonuclear leucocytes, however, are usually very scanty, these apparently leaving the marrow in the hours preceding death. The condition of the eosinophiles varies somewhat, but they do not disappear from the marrow as they do from the blood in this disease, nor, on the other hand, is there evidence that a special accumulation takes place in the marrow. The giant-cells are sometimes distinctly more numerous than normal, of large size, and with nuclei showing great condensation of the chromatin with irregularities in shape;[3] some are degenerated. Once or twice I have found multiple mitosis in those cells. It is difficult to state the significance of the

[1] Pl. XIII, fig. 2. [2] Pl. XII, fig. 2. [3] Pl. XII, fig. 6.

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change, but observations in other diseases, and experiments on animals, show that such increase is not a constant change when there is increased formation of neutrophiles.

In some cases, as already mentioned, the marrow is red, and in these the fat is usually less diminished. For both reasons, therefore, there is a less proportionate increase of the myelocytes. In view of what may be observed in other severe infections, I think that this condition may be due to the severity of the toxæmia, and to the entrance of myelocytes into the general circulation before death, and may thus be an example of what happens to a great degree in smallpox. I may mention that it was most marked in a case of alcoholic pneumonia. I could find no peculiarity in the pneumonic consolidation which could be brought into relationship with this condition, but it would be of special interest to observe whether it occurs specially in cases with leucopænia and with myelocytes in the blood before death. Unfortunately I have not had an opportunity of investigating this point.

The marrow in the femur shows varying degrees of change. In cases with fatal results about the tenth day, one may state that the upper third of the femur shows distinct alteration. By this is meant that the red marrow has extended downwards for this distance, although it may still contain a large proportion of fat. The changes found in the extending marrow have been described above.

The marrow in variola.—The condition of the marrow in smallpox is one of much interest, inasmuch as the leucocytes in the blood in this disease show changes of a different kind from those obtaining in most infections. The blood has been the subject of careful investigation by Weil, Courmont and Montagard, and Ferguson, and the following may be given as a brief statement of the important facts. The leucocytosis, which is most marked in severe cases running a favourable course, is characterised by a marked increase in the proportion of the lymphocytes, especially those of larger size, the proportion often reaching as high as 60 per cent. The neutrophiles always show a percentage decrease though the total number is usually above normal, especially when the leucocyte number per c.mm. is high. In the rapidly fatal cases, especially those of the hæmorrhagic type, there is leucopænia, often of marked degree,

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and this may be associated with the appearance in the blood of myelocytes, neutrophile and eosinophile, and also of nucleated red blood-corpuscles. My assistant, Dr. Ferguson, has found that myelocytes may sometimes number as much as 15 per cent. of the cells in the blood; they, in fact, occur in greater numbers than in any other acute infection. It is further to be noted that in the skin lesions the leucocytes show a general correspondence with the blood-leucocytosis, most of them being of the mononuclear variety, and comparatively few neutrophiles being present. Observations on the marrow have been comparatively few. Golgi, who was the first to give an account, distinguishes different types in the suppurative and hæmorrhagic varieties. In the former the marrow is pinkish and fairly firm and abundant, and is characterised by a large proportion of colourless cells; in the latter it is of a deep red colour, almost fluid, and contains comparatively few leucocytes but a large proportion of red corpuscles. He considered that in the one case the reaction was chiefly on the part of the white cells, in the other of the red. Chiari describes a condition which he calls osteomyelitis variolosa, and which is characterised by the occurrence of foci of cellular proliferation and a certain amount of necrosis. This change he compares to the characteristic lesion in the skin. Quite recently Weil has described the state of the marrow in different types of smallpox, and finds that the reaction is practically the same in all, the cells present being nearly all of the mononuclear class, and a large proportion being non-granular. Polymorphonuclear leucocytes are almost absent, and there is little or, it may be, no extension of the marrow in the long bones. Courmont and Montagard come to practically the same conclusion. I shall first give an account of my own observations, and shall then discuss how far they agree with those mentioned.

I have examined the marrow in eleven cases of smallpox; of these six were hæmorrhagic, three were semi-confluent, one was discrete and of severe nature, and one was comparatively mild, pneumonia occurring as a complication in the last. The femur was examined in five; in two of these there was no extension of the red marrow, though in one of these there were some scattered hæmorrhages in the fat; in the other two there was a slight growth of red marrow downwards from the epiphysial line,

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and also general congestion of the fat. The condition of the marrow in the ribs may be taken as the standard. The marrow here varies in character in different cases; in some it is not unlike normal marrow, being merely somewhat softer in consistence and redder; in others it is markedly changed, being of a deep red colour and almost fluid, and usually containing small granular particles of paler colour. In most cases I have found on microscopic examination that these particles are mere cellular masses, sometimes with an admixture of coagulated fibrin; in one or two instances there was a trace of degeneration in their centre, but I have never seen any of the larger foci as described by Chiari. This red and very soft marrow is that usually found in hæmorrhagic cases, but may also be met with in the other types.

The results of microscopic examination of film preparations and of sections may be stated as follows. (I may note that the marrow is often so fluid that when dropped into formol-alcohol it does not cohere in masses, but merely spreads out as a film on the surface of the fluid. In such cases, however, if the drops are placed on a piece of thin paper and this is then gently put into the fluid, they retain their form, and sections can be obtained.) The changes vary, of course, in degree, but the most characteristic feature is the diminution in the proportion of the cellular elements with increase in the amount of blood. The fat is not markedly reduced, being, as a rule, slightly less abundant than normal.[1] The neutrophile myelocytes are usually diminished in number, sometimes to a marked degree in hæmorrhagic cases; mitotic figures may occasionally be seen, but they are few in number. In cases where the marrow is pinkish the myelocytes may be relatively numerous,—in fact, more so than in the normal state; this, however, is the exception. Some of the myelocytes may be degenerated, but this is by no means a marked change. Polymorphonuclear neutrophiles are practically absent; in fact, it may sometimes be impossible to find a single well-preserved example. Eosinophile myelocytes are also scanty, though, perhaps, they are proportionately less diminished than the neutrophiles; here and there may be found a polymorphonuclear eosinophile. Non-granular myelocytes are relatively less diminished, but I have found no evidence of active proliferation of these cells. There are, however, often to be

[1] Pl. XIII, fig. 4.

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found collections of larger cells which I consider to be in all probability endothelial cells, and probably representing the proliferative process seen in larger foci described by Chiari. They are evidently the result of toxic action on the stroma of the marrow. Giant-cells are few in number, many are of relatively small size, and most are degenerated. As stated above, there is a large amount of blood, and, although actual hæmorrhages may be present, most of it is contained in the widened vascular channels. Nucleated red corpuscles appear in some cases to be more numerous than normal, but this is probably only an appearance due to the diminution of other cells; I doubt whether there is a distinct actual increase. I may add that in the newly formed marrow in the femur I have found practically the same changes as in other conditions; and although the neutrophile myelocytes may be rather less abundant, still their proportion is comparatively large. It is also of importance to note that this young marrow may show less depletion than the marrow in the ribs.

My general conclusion with regard to these changes is that in smallpox a certain amount of neutrophile reaction may be present, but that in most cases it is absent or masked by other phenomena, there being a diminution of the cellular elements, especially of the neutrophile myelocytes, and a great increase of blood, the widened vascular channels filling the space formerly occupied by these elements. There may therefore be said to be a depletion of the marrow, and I think there can be no doubt that its cells are carried off by the blood-stream. This depletion is most marked in the very severe cases; and, as stated above, myelocytes and also nucleated red corpuscles are found in considerable numbers in the blood in such conditions. I may also add that they may be found in still larger numbers in the splenic pulp (*vide infra*). The displacement of the marrow-cells is probably due to disturbance of the delicate structural arrangements of the marrow. It occurs in other severe infections, both in animals and in the human subject, but in none of these have I found it to so great a degree as in smallpox. I have found no distinct evidence that the increase of the lymphocytes is to be associated with the changes in the marrow; these probably being produced in the lymphoid tissues proper, as in the normal condition. The condition in a mild case complicated by

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pneumonia is worthy of remark, as here also there was relative diminution of the marrow-cells; the fat was, however, also diminished. The condition in the lung corresponded to the stage of grey hepatisation, and the cells in the pulmonary alveoli were chiefly polymorphonuclear leucocytes, as in ordinary cases. In spite, then, of the depleted condition of the marrow there had been, during life, an increased production of neutrophiles. It is difficult to explain the association of the two conditions, but depletion was probably a terminal phenomenon. Ferguson has noted that in smallpox there is often a want of the usual emigration of polymorphonuclear leucocytes around the pyogenic micrococci in the tissues, and there is no doubt that the smallpox poison has a pernicious action on these cells. In the present case, however, this action had not interfered with their emigration from the pulmonary vessels, and had only manifested itself by increasing the depletion in the marrow which is sometimes seen in cases of pneumonia. Unfortunately an examination of the blood was not made, but only a very small number of myelocytes were present in the spleen.

Weil draws a parallel between the condition of the blood and that of the marrow in smallpox, and points out that it is in the cases where there has been marked leucocytosis that there are most cells of the leucocyte class in the marrow. These, however, are not the most severe cases, and he overlooks the significance of the fact that when myelocytes are most numerous in the blood their number is most diminished in the marrow. From what has been stated above, there are manifest objections to his comparison of the leucocyte picture in smallpox with that in leucocythæmia (*vide* also p. 396). Golgi's distinction in the two types of the disease has a measure of truth in it, but the difference arises not from the nature of the reaction, but from the severity of the infection.

The gelatinous marrow.

Although this change does not come under the heading of "reactions," but is of a retrogressive nature, a few facts may here be given regarding it. Its occurrence has long been recognised, and we find the earlier writers on the subject speaking of three types of marrow in the long bones, viz. fatty, gelatinous, and lymphoid. The stages of change can be

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well followed in the case of the fatty marrow of the femur. Here and there between the fat-cells there appears an interstitial substance of homogeneous appearance, which grows at the expense of the fat-cells. The latter gradually become smaller and smaller, and ultimately disappear in the homogeneous material; sometimes the appearances are as if the fat-cells had their contents replaced by serous fluid, and then became merged in the gelatinous substance. Large areas of homogeneous appearance are thus formed, in which there are present only scattered nuclei, often of small size and angular in shape. The gelatinous substance does not give the reactions of mucin (Roger), though it is probably an albuminoid of the same class, and apparently formed from the lymph and certain derivatives of fat. This change also occurs in the red marrow of the ribs, etc., where it starts around the scattered fat-cells there present, and ultimately increases, so as to replace to a large extent the cellular elements. In this way the marrow of the short bones may come to have a red, gelatinous character. In two cases so high a degree had this reached that the cells only occurred in relatively small masses in relation to the blood-channels; one was a case of chronic Bright's disease, the other of marasmus in an adult without assignable cause.[1] The change, though primarily in the interstitial tissue, may thus be associated with marked atrophy of the cellular elements. In certain conditions, *e. g.* in suppuration with extreme emaciation, we have an association of gelatinous marrow and leucoblastic reaction, though the latter is less marked than it would be in an ordinary case.[2] It is probable that the gelatinous substance interferes with the cellular hyperplasia when there is call for reaction, and it may be that the cellular tissue may retrogress and be replaced by this material.

When the conditions of occurrence of this change are considered, the all-important factor seems to be inanition. There is always more or less emaciation, and often the degree of the change is proportional to the diminution of the subcutaneous fat. Roger has produced the alteration experimentally by starving rabbits for ten days; and I have found it accidentally in two rabbits, in both of which there was great emaciation, the cause in one case being apparently an extensive cysticercus infection. My colleague,

[1] Pl. XIII, fig. 5. [2] Pl. XIII, fig. 6.

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Professor Stockman, has been able to produce the change by the administration of calomel and of arsenic in comparatively large doses, although smaller doses cause a cellular hyperplasia. In his experience there is always much emaciation along with it.

Summary.—(1) The leucoblastic condition or the neutrophile reaction in the human subject is shown both by the increase of the cellular marrow at the expense of the fat in the small bones and by its extension into the fat of the long bones. In the new tissue there is a formation of all the elements of the marrow, but the increase of the neutrophile myelocytes with increased proliferative activity is the most important feature. The granules of these cells are often more distinct than normally. (2) In common with all defensive reaction, the myelocyte hyperplasia is within certain limits in proportion to the extent and duration of the infection. (3) When the infection is specially severe, leucopenia occurs, and the myelocytes may leave the marrow and appear in the blood-stream. The marrow then contains a relative excess of blood. This depleted condition is specially seen in severe smallpox. (4) In the extension of the marrow the cells which appear first seem to be neutrophile myelocytes, and I have found no distinct evidence that a transformation of non-granular into granular myelocytes plays a part in increased supply of neutrophile leucocytes. (5) The eosinophile cells in the marrow do not increase in the same proportion as the neutrophiles. Certain facts, however, suggest a post-inflammatory increase. (6) The giant-cells in severe acute infections, *e. g.* acute pneumonia, may be increased in size and number; in other cases they may be little altered. The extension of the marrow in the long bones is usually attended by new formation of these cells. (7) Whilst the formative function of the marrow is thus greatly exaggerated in infections, there is, on the other hand, comparatively little phagocytosis on the part of its cells, this being chiefly exerted towards red corpuscles and occasionally leucocytes; the phagocytic cells are non-granular.

The pathological alterations of the marrow may be stated thus:

(1) Changes in the lymphatic and medullary forms of leucocythæmia, these being sometimes followed by granular or fatty degeneration of the cells. In the former there is an infiltration with lymphocytes and displacement of the marrow elements; in the latter there is a medullary hyperplasia.

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(2) Reactive changes.

a. Leucoblastic: The *neutrophile* reaction is by far the most important; it may be followed by a depleted condition, or this may occur independently; in all probability also an *eosinophile* reaction; possibly a *hyaline* reaction will be established.

b. Erythroblastic: The *normoblastic* type after hæmorrhage; and the *megaloblastic* type in pernicious anæmia, also in bothriocephalus anæmia.

(3) Degenerative or retrogressive changes.

a. The *gelatinous change,* the chief factor in its causation appearing to be inanition.

b. The *fatty change,* the red marrow being replaced by adipose tissue, observed in a case of idiopathic anæmia by the author.

2. *The spleen.*

I shall here simply describe the most important changes in the spleen in infections, so as to bring them into contrast with those in the marrow.

(1) *Destructive processes.*—In the first place, the phagocytic activity of the cells in the pulp constitutes an outstanding feature. The cells concerned here, just as in the case of lymphatic glands, are non-granular cells, partly hyaline leucocytes and partly endothelial cells. Regarding the important part played by the latter there can be no doubt, as one can observe them becoming swollen up and desquamated from the reticulum and sinuses. Mitotic figures are also to be observed in these cells, though I think it is doubtful whether division occurs after the cell manifests its phagocytic properties. The hyaline leucocytes also become increased in number, and mitotic figures, I believe, are to be observed in them also, though it is often difficult to determine whether a cell undergoing division is a hyaline leucocyte or a small endothelial cell. We may thus state that there occurs in many infective diseases a great increase in non-granular phagocytes. It is well known that in these conditions the spleen undergoes enlargement, and may present various tints, from a deep red to a pale pink. The colour of course depends upon the relative proportion of leucocytes and red corpuscles. The swelling is in part due to accumulation of more or less damaged elements, and a destruc-

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DESCRIPTION OF PLATE XII,

Illustrating Professor Robert Muir's communication on the Reaction of Bone-marrow in Infections. (Page 379.)

FIG. 1.—Section of normal rib-marrow of an adult, showing the relative proportion of cellular elements and adipose tissue. × 100.

FIG. 2.—Section of rib-marrow from a case of acute pneumonia, showing the great cellular hyperplasia (neutrophile reaction) and diminution of the adipose tissue; to contrast with fig. 1. × 100.

FIG. 3.—Section of the margin of the newly formed red marrow of the femur, from a case of acute pneumonia, showing the widening of the vascular channels and accumulation of myelocytes, etc., around them. × 100.

FIG. 4.—Section of another portion of the same marrow as in fig. 3, showing a more advanced stage of formation. × 100.

FIG. 5.—View, under higher power, of newly formed marrow in femur in a case of suppuration, showing the various cellular elements present. × 300.

FIG. 6.—Section of marrow of rib in a case of pneumonia, showing the cellular hyperplasia; also giant-cells with condensed chromatin. × 300.

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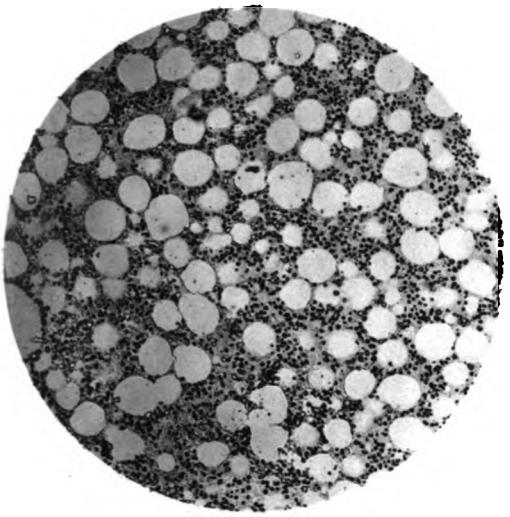

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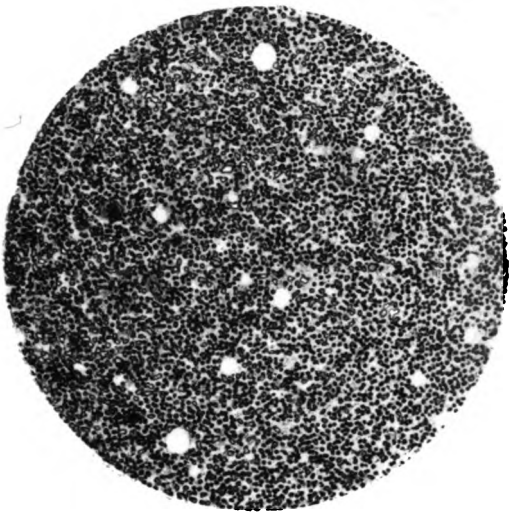

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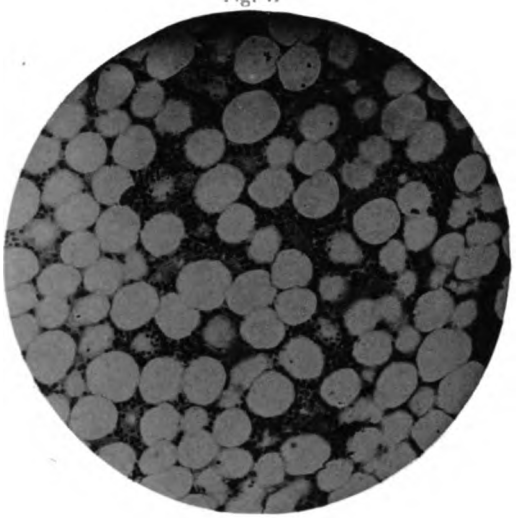
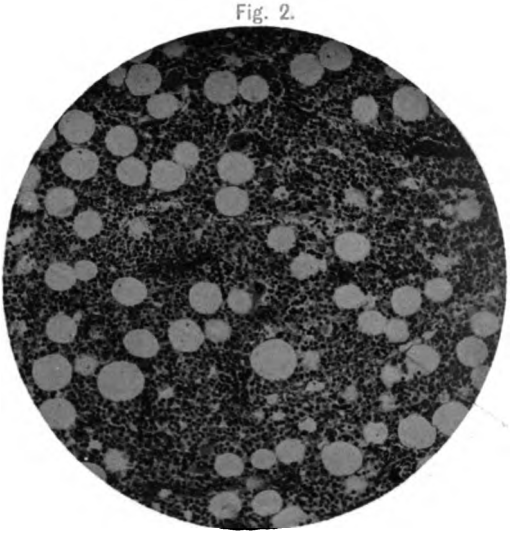


Fig. 3.



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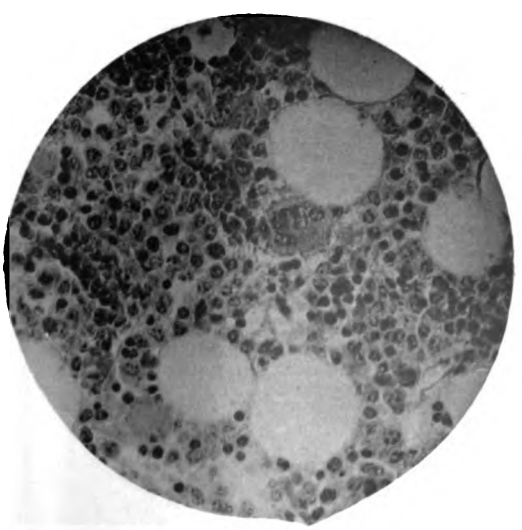

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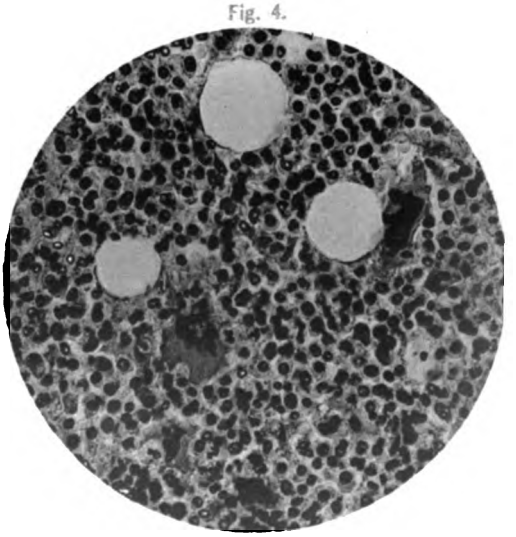

Fig. 6.

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DESCRIPTION OF PLATE XIII.

Illustrating Professor Robert Muir's communication on the Reaction of Bone-marrow in Infections. (Page 379.)

FIG. 1.—Film preparation of marrow of rib in a case of empyema, showing numerous myelocytes with transitional forms to polymorphonuclear leucocytes (two myelocytes undergoing mitotic division); also two eosinophile myelocytes, nucleated and ordinary red corpuscles. × 600.

FIG. 2.—Section of newly formed marrow of femur in a case of suppuration, showing the preponderance of finely granular myelocytes, in one of which is seen a mitotic figure with achromatic spindle. × 1000.

FIG. 3.—Another portion of same marrow as in fig. 2. A somewhat triangular, young giant-cell undergoing multiple mitosis (three asters of a tetraster) is seen about one eighth of an inch below the edge of the highest fat vesicle and slightly to the left of the mid-line. × 600.

FIG. 4.—Section of marrow of rib in a case of hæmorrhagic variola, showing the marked diminution of cellular elements, along with increased amount of blood and some diminution of adipose tissue. × 100.

FIG. 5.—Section of marrow of rib from a case of chronic Bright's disease with extreme marasmus, showing advanced stage of gelatinous transformation. × 100.

FIG. 6.—Section of marrow of femur from a case of malignant disease and chronic suppuration, showing a slight amount of cellular reaction, along with gelatinous change. × 100.

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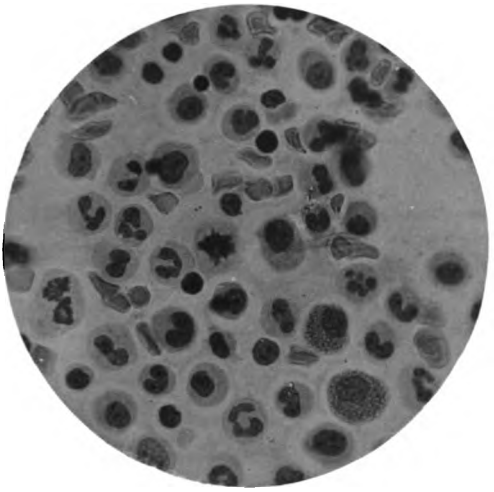

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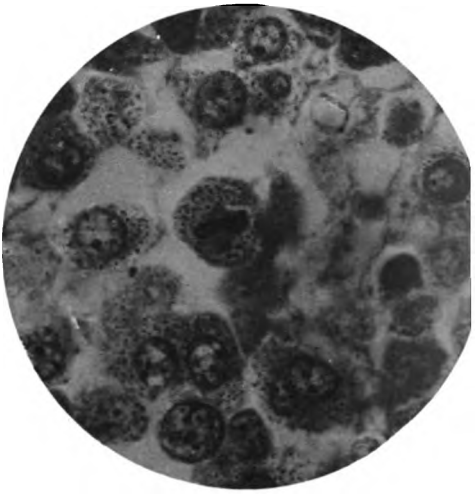

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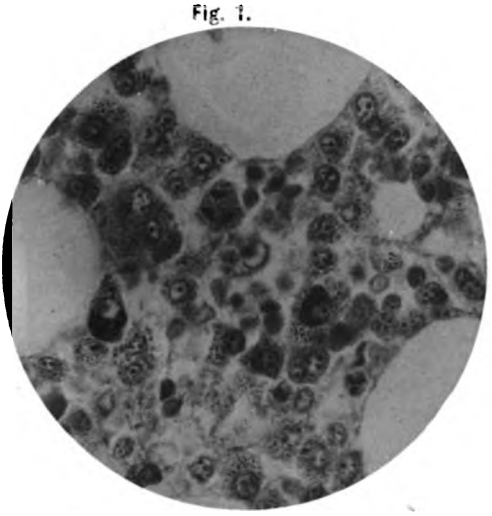

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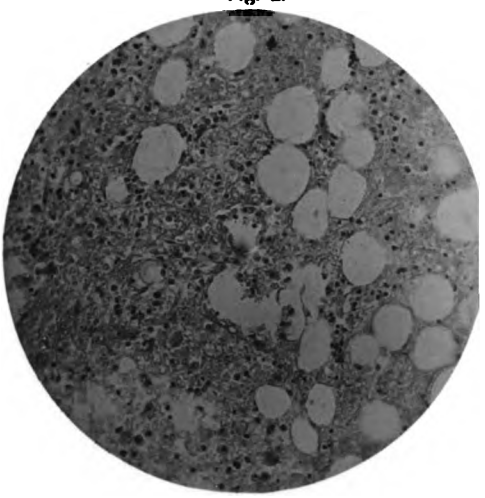

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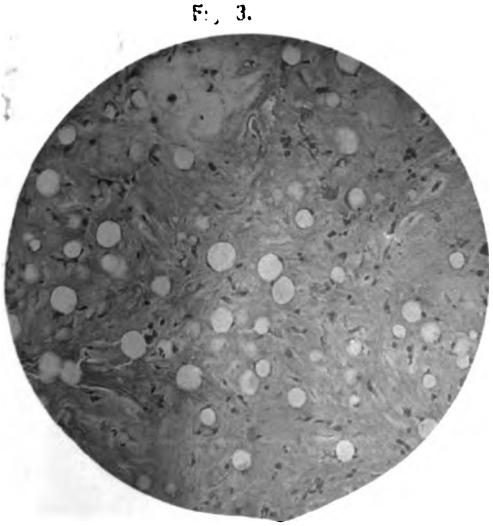

Fig. 5.

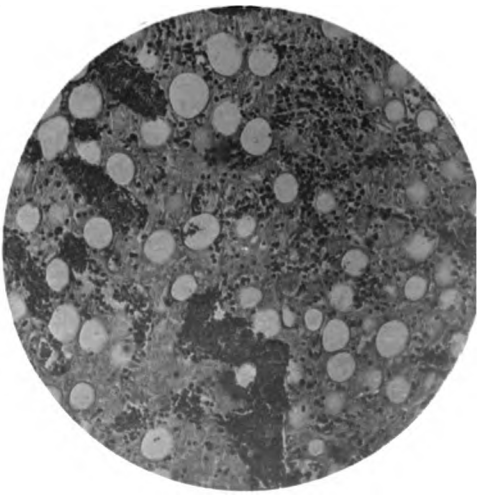

Fig. 6.

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tion of these takes place to a great extent. In addition to bacteria, the elements which are chiefly destroyed in this situation are neutrophile leucocytes and red corpuscles, though other degenerated cells are also ingested by the phagocytes. Both of the former cells are taken up by the phagocytes, but to a varying extent in different animals. Thus phagocytosis is much more marked in the spleen of the rabbit than in the human spleen. One can often see in the rabbit's spleen in infections non-granular cells containing as many as twenty or more red corpuscles and half a dozen neutrophile leucocytes in various stages of disintegration. This process, especially as concerns the red corpuscles, is most marked around the sinuses, though it also occurs throughout the pulp. The neutrophile leucocytes also undergo an extra-cellular digestion. I have observed this in the rabbit, and have traced all stages down to disappearance of the cell, the structural changes corresponding exactly with those when neutrophiles are ingested by the phagocytes of the peritoneal cavity. A similar process takes place in the human spleen. There is no doubt that extra-cellular disintegration of the red corpuscles also takes place to a large extent. These facts therefore go to show that the spleen plays an important part in the destruction of red corpuscles and leucocytes, partly after ingestion by phagocytes, and partly outside of these cells, probably by means of digestive ferments.

(2) *Presence of myelocytes, etc.*—Another point of importance in infective conditions, especially when these are of severe degree, is the presence of myelocytes in the splenic pulp. Recent observations show that the presence of these cells in the peripheral blood in such diseases is much more common than was formerly supposed, and in the lower animals they appear much more readily than in the human subject. Their occurrence in large numbers in the blood in the severer forms of small-pox, especially in those of hæmorrhagic character, has already been referred to (p. 387). And I have found in experimental infections that whenever they are present in the blood they occur in proportionately greater numbers in the spleen, the appearance being as if this organ endeavoured to remove them from the blood. Observations on the human spleen by my late assistant, Dr. Logan Taylor, show that the occurrence of these cells in small numbers is comparatively common in infective

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conditions. Their presence both in the blood and in the spleen is usually associated with that of nucleated red corpuscles. What the fate of myelocytes within the pulp is I cannot definitely say, as their appearance there is so often a terminal phenomenon that they are usually in a comparatively well-preserved condition. I have once or twice observed them undergoing mitosis, but I have never seen any evidence of phagocytic function. Their presence, I believe, is to be regarded as an escape from the marrow as the result of disturbance of its delicate structure, as already described. It is difficult, apart from this view, to explain the almost invariable concomitance of these cells with nucleated red corpuscles. I have considerable difficulty in accepting the interpretation put upon the appearance of nucleated red corpuscles in the blood by French writers, namely, that it represents an increased regeneration following upon the destruction of red corpuscles in infective processes. The fact that their number has no relation to the oligocythæmia, and also the fact that they often appear in increased numbers just before death, are to my mind distinctly against this view.

(3) *Proliferative changes.*—I have already mentioned the occurrence of mitosis in endothelial cells and in hyaline leucocytes in the pulp. I may add, however, that these are relatively not numerous, and in the human spleen may only be found after careful search; the marrow and splenic pulp often indeed present a striking contrast as regards cellular multiplication. There may, however, sometimes be observed another proliferative change at the periphery of the Malpighian bodies. It can be well studied in the spleen of the rabbit, and has had an important significance attached to it by certain French writers, especially Dominici and Bezançon.

This consists in the proliferation of cells there and the formation of a distinct zone around the Malpighian body, so that the latter undergoes apparent enlargement. The cells concerned are of larger size than lymphocytes, and have relatively abundant protoplasm, which has a distinctly basophile reaction. This is specially well seen on staining with methylene blue. They can be seen lying between delicate fibrils, which run in a more or less concentric manner around the Malpighian body, and often show variation in form in conformity with their position between the fibrils, being often oval or slightly tailed. The active mul-

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tiplication of these cells is shown by the occurrence of mitotic figures, and I think there is no doubt that as they increase in number they move outwards into the pulp. This is a condition distinctly pathological, as there is only slight evidence of such a zone in normal conditions. The question is, What do these cells represent? It may be that they are formed from lymphocytes, under the influence of abnormal substances in the pulp; or they may really be derived from small cells of the endothelial class situated on the delicate fibrils at the periphery of the Malpighian bodies. A special interpretation of their significance has, however, been made by the French writers referred to, viz. that they represent a layer of potential myelocytes, *i. e.* a layer of non-granular cells which, under the stimulus of toxines, multiply and acquire neutrophile granules. The myelocytes thus formed pass into the pulp and form polymorphonuclear leucocytes. There thus occurs what is called a "myeloid transformation of the spleen." Great care must be exercised in accepting such a view, though it is not sufficient to direct *a priori* reasoning against the existence of a layer of undifferentiated cells in the adult. There is no doubt that these basophile cells formed at the periphery of the Malpighian bodies pass into the pulp, and there is no doubt that myelocytes may be present, lying side by side with these cells, though they are also present throughout the pulp. But I have not found sufficient evidence that the one class is derived from the other, and the position of the myelocytes may quite well be explained by a transference by the blood-stream. I may say also that the drawings given by Dominici, though accurately representing the zone of basophile cells as I have seen them, are not conclusive as regards their transformation into myelocytes. It is equally probable that the non-granular cells in question pass into the pulp as such, and there act as phagocytes, the process corresponding with what is seen in the lymph-sinuses of lymphatic glands.

I consider, then, that this question of myeloid transformation must be held to be an open one; in considering it the following facts must be kept in view:—(*a*) Where there is a long-continued drain on finely granular leucocytes, *e. g.* in suppuration with leucocytosis running a natural course, there may be no alteration of the above nature in the spleen. I have, for example, found a most extensive hyperplasia of the myelocytes in the rabbit's

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marrow in association with an atrophied condition of the Malpighian bodies in the spleen. Thus, even if the myeloid change takes place, its occurrence is not constant, or, in other words, is not called into action by the increased demand for finely granular leucocytes *per se*. (*b*) As mentioned above, in the condition where myelocytes are most numerous in the spleen and in the blood, viz. in hæmorrhagic smallpox, we find that the myelocytes in the marrow are diminished in number. The number of myelocytes in the spleen has much more relation to the intensity of the poisoning than to the amount of leucocyte reaction in a given case. On these grounds their presence in this organ, usually in association with nucleated red corpuscles, appears to represent an escape from the marrow. Probably the proliferation of basophile mononuclear cells at the periphery of the Malpighian bodies represents a reaction resulting from the action of abnormal substances in the pulp on these structures.

In connection with this subject I may mention that Roger, Weil, Dominici, and other French writers believe that the faculty of undergoing this myeloid transformation is very wide-spread in the connective tissues of the body. Thus they regard in this light the cellular collections around the lymphatic glands and the cellular foci in various organs in smallpox, as well as the cellular infiltrations of the tissues in medullary leucocythæmia. That is to say, in the conditions mentioned the cells are formed *in situ* from pre-existing cells, and do not come from the blood-vessels by emigration or by rupture of the capillaries. The histological examination of these changes, in my opinion, gives no support to such a view.

With regard to increased proliferation of lymphocytes in the central parts of the Malpighian bodies in infective conditions I prefer not to make a definite statement, as I am still investigating the matter. Sometimes the areas of lymphocytes seem increased in extent, and mitoses more numerous than in the normal state. Sometimes, however, these changes are absent, and I have not been able to bring them into definite relation with the occurrence of lymphocytosis in the blood.

3. *The lymphatic glands.*

Exact knowledge regarding increased formative activity in the germ-centres of lymphoid tissue apart from a local infec-

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tion is still wanting. In comparatively few conditions does a lymphocytosis in the blood occur; and although an increase in the larger mononuclear cells is more common, the relation of all the cells of this group to the lymphocytes cannot be regarded as fully cleared up. In smallpox, however, a lymphocytosis is met with, but in this disease we find so frequently marked signs of reaction in the sinuses and lymph-paths in the glands, apparently secondary to the skin lesions, that the lymphocytosis in the blood may possibly be due to what we may call the sum total of the local reactions. It is to be noted, however, that in the skin lesions the chemiotactic agencies seem to affect the smaller mononuclear leucocytes. Ehrlich considers that lymphocytosis is produced by increased lymph-flow through large lymphatic areas; probably to this we may add the wide-spread distribution of irritating substances in lymph carried to the lymphoid tissues. Labbé has found that in the case of local infections there may occur, at certain periods, increased size and activity of the germ centres; and Stiles has shown that in cancer of the breast there is met with increase of lymphoid tissues in the axillary glands, some of which may normally be largely occupied by fat. At present we can scarcely state that abnormal substances in the blood act upon the lymphoid tissues generally and lead by direct stimulation or otherwise to a lymphocytosis in the blood. The absence of the mechanism for a direct chemiotactic action from the blood, notably present in the case of the marrow, has already been pointed out.

Although local conditions may lead to increase of lymphoid tissue, we find the enlargements of lymphatic glands occurring in infections are due to other causes. In fact, the reactions correspond to those in connective tissue generally, and their chief features are due to two circumstances, viz. first, that bacteria and various abnormal elements are arrested in the glands; and secondly, that there is an abundant provision for phagocytosis. To speak generally, in one group of cases the granular cells are chiefly concerned, in another the non-granular.

In an acute condition produced, for example, by staphylococci, the neutrophile cells emigrate from the vessels and infiltrate the tissue of the gland just as they do an ordinary connective tissue. They appear first around the vessels in the

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more central parts of the gland, in the cords of lymphoid tissue, and afterwards spread to the lymphatic paths, in which they may occur in enormous numbers. The lymph-follicles at the periphery are less affected, but in a severe affection, such as plague, these also are overrun by neutrophile leucocytes, the lymphocytes behaving in an apparently passive manner. Other cells, however, play an important part, especially when the affection is moderately mild, or towards the close of a severe affection. These are the endothelial cells, the cells on the reticulum of the sinuses, and also the fixed cells within the lymphoid tissue proper. These cells become swollen up, rounded or oval in shape, and ultimately become free. They undergo division by mitosis, those most frequently seen in process of division being generally attached to connective-tissue fibres, the walls of the sinuses, etc. The large hyaline cells in the lymph play a similar though less important part. All these cells behave as active phagocytes and ingest red corpuscles, polymorphonuclear leucocytes, *débris* of cells of all kinds. In fact, a close parallel, as regards behaviour, can be drawn between them and the cells of the peritoneum; and just as in the case of the peritoneum an apparently complete return to normal may take place after considerable desquamation of the endothelial cells with active phagocytosis on their part, so also with lymphatic glands the cells which have been lost may be restored, and ultimately no evidence of the inflammatory condition may remain (Labbé).

In some conditions, however, there may be practically no emigration of neutrophile leucocytes from the blood-vessels, and the phenomena of reaction are almost entirely confined to the fixed cells along with the mononuclear leucocytes. This is notably the case in typhoid fever, where the endothelial cells of the lymph-paths undergo extensive multiplication and desquamation, so that these paths are distended with the shed cells. To this cause the enlargement of the glands is chiefly due. In the earlier stages, or in milder cases, the phagocytic property of these cells is well marked; but where toxic action is more severe they become necrosed, and present a structureless appearance. Such a process is not confined to the lymphatic glands, but, as Mallory has pointed out, also occurs along the lymphatics in the intestinal wall and in various other parts. We have, therefore,

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evidence here of a toxine which acts markedly on these fixed cells (potential phagocytes), but which usually has little or no chemiotactic action on the neutrophile leucocytes.

In smallpox I have observed corresponding changes in the lymphatic glands—changes which are most marked in the severe discrete and confluent cases. From the skin lesions there pass to the glands numerous red corpuscles, leucocytes, and their remains, and one sees along the lymph-paths very marked phagocytic reaction. In the earliest stages one can see the enlarged endothelial cells clinging to the reticulum, some of them undergoing mitosis, whilst later the paths are distended with these cells, which often reach a considerable size, and which contain in their interior red corpuscles and leucocytes in various stages of disintegration. The sinuses and lymph-paths may thus be distended with these cells while there is practically no emigration of neutrophiles from the vessels.

In certain of the lower animals eosinophiles are normally present in the lymphatic glands, especially in their central parts, and in the human subject they are present in considerable numbers in a variety of abnormal conditions. This is often well seen in smallpox, and it would appear as if certain products of tissue disintegration acted chemiotactically on those cells; so also in some varieties of "malignant lymphoma."

I may add that a study of the lymphoid glands in inflammatory conditions lends no support whatever to the view that lymphocytes become transformed into polymorphonuclear neutrophiles.

General considerations.

At the commencement of this paper I pointed out that certain regions in the tissues were set apart for the proliferation of leucocytes, whilst other parts were specially adapted for their phagocytic properties. This distinction is emphasised by a study of the reactions in infections, the most important qualification being that, in certain situations, *e. g.* spleen-pulp, lymph-sinuses and paths, what may be called the "local phagocytes" undergo multiplication by division.

The facts above stated clearly bring out into prominence the finely granular (neutrophile or amphophile) leucocytes as a class

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possessing distinct characteristics. The following points may be mentioned in this connection:

a. Their normal distribution is definitely restricted,—in fact, it corresponds with that of the red corpuscles, while the mother-cells of both (myelocytes and erythroblasts) are present in the bone-marrow. In saying that the neutrophile leucocytes are normally confined to the blood-stream I, of course, except such situations as mucous membranes, tonsils, etc., where they emigrate in the presence of bacteria. My own observations show that they are absent from the lymphatic trunks, from the lymph-paths in lymphatic glands, and from the thoracic duct; and as they cannot be found in the connective-tissue spaces, one must conclude that if they emigrate from the blood-vessels in normal conditions they must be rapidly destroyed.

b. They constitute the most rapidly applied and most extensive means of defence—no other form of cell can be added to the tissues in such large numbers and in so short a time. This is well seen in acute suppurative conditions, and needs no further remark. Corresponding with this, the mother-cells have a most remarkable power of proliferation; in no other class of cell may so many mitotic figures be observed in the human subject *post mortem*. The phagocytic function appears to be absent, or at least in abeyance, in the myelocytes. We have further to note the extension of the tissue occupied by these cells.

c. The comparatively constant size of these cells is worthy of note; this is seen in the case both of the neutrophile leucocytes and myelocytes. It would appear as if provision for additional defence was always supplied by increase in numbers, not in size. The non-granular phagocytes, on the other hand, may undergo great enlargement in pathological conditions.

d. The facts established with regard to local emigration of the finely granular cells and with regard to blood-leucocytosis can readily be explained by chemiotaxis, in the one case acting on the blood from the tissues, and in the other acting on the marrow from the blood.

The laws governing the movement of the *eosinophiles* closely correspond so far as increase of their number in the tissues and in the blood is concerned, and Dominici has recently described the increase of the eosinophile cells in the marrow in association with eosinophilia in the blood. I have mentioned above the same

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change as a sequel to long-continued suppuration. Further observations are no doubt necessary, but there can be little doubt that the analogy between the eosinophiles and neutrophiles will be found to be complete in all important points. There is this difference, however, viz. that eosinophiles may occur extra-vascularly under normal conditions (*e. g.* in serous cavities, lymphatic glands, etc.), and more so in the lower animals than in the human subject. A connective-tissue origin of eosinophiles is not excluded, but hitherto the only forms which I have seen undergoing mitosis are the large mononuclear forms in the marrow.

Many facts regarding the movements of lymphocytes and hyaline cells are still undetermined, and, to speak generally, there is much doubt as to the relationship of the different varieties of "mononuclear leucocyte." I shall merely refer to some of the properties of the non-granular phagocytes—hyaline leucocytes, endothelial cells, and connective-tissue cells,—and contrast them with the granular cells. These cells are present practically everywhere in the tissues, and with the exception of cases where the hyaline leucocytes emigrate from the vessels, sometimes thereafter multiplying in the tissues (I might mention as an example acute interstitial nephritis, well described by Councilman), the defence depends on the cells present locally. The multiplication and accumulation of these cells is *relatively* a slow process, and accordingly this form of reaction is specially suited to the subacute and chronic infections. Some bacteria, or rather their products, act chemiotactically on these cells and not on the neutrophile leucocytes, *e. g.* typhoid, tubercle in the human subject, etc. All three varieties of the non-granular phagocytes may undergo great hypertrophy in discharging their function, while marked lobulation of the nucleus or a multinucleated condition may occur. Further, the chief elements of the blood, viz. red corpuscles and neutrophile leucocytes, especially when in a degenerated condition, act chemiotactically upon these cells and undergo digestion within them. This phagocytosis of the elements of the blood can be seen well in the lymphatic spaces of connective tissue, and especially in the serous cavities and in the lymph-paths of lymphatic glands; it also occurs intra-vascularly, *e. g.* in the splenic pulp and to a less extent in the bone-marrow. I may add that phagocytosis

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of neutrophiles by the non-granular cells is especially seen after the former have done their work—after the granular attack has been successful.

Although these different forms of non-granular cells behave in a somewhat similar fashion so far as their phagocytic properties are concerned, and may become altered in appearance so as to be indistinguishable from one another, it does not follow that they can be transformed the one into the other. The phagocytic property is one which in course of development appeared prior to the other characters, *e. g.* special functions associated with differentiation of structure.

All three classes of non-granular cells mentioned are doubtless subject to chemiotactic influence. As concerns the connective-tissue cells, this has been well brought out by Ribbert in the case of the pigmented cells of the iris. After injection of sterile agar into the anterior chamber of the eye, he found that the pigmented cells moved towards it without there being any appreciable damage to the iris, and before mitosis appeared in the cells in question. And I think it highly probable that the so-called desquamation of endothelial cells is not entirely due to damage, but in part, at least, represents a movement in response to stimulus. Mitosis is commonly to be found in the endothelial cells, and also in the connective-tissue cells, both when in their normal situation and after they have become free. It is, however, beyond the scope of this paper to discuss whether this is due to a "direct formative stimulus," or whether it is the result of disturbance of the normal relationships of these cells.

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February 18th, 1902.

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39. *Fibrinous cast of gall-bladder in cholelithiasis.*

By H. D. Rolleston.

The patient, a woman aged 52, who had never had jaundice or biliary colic previously, was suddenly seized with pain on the right side of the abdomen and vomiting. On admission to St. George's Hospital two weeks later a tumour of stony hardness was found in the right iliac fossa, separated from the liver dulness by a zone of resonance. Laparotomy was performed by Mr. Allingham, and revealed a greatly enlarged gall-bladder, united by adhesions to adjacent parts. On opening the gall-bladder, a single calculus, rather larger than a walnut, enclosed in a membranous sac was removed. This membrane was easily detached from the walls of the gall-bladder, and was brown in colour and not unlike a dysmenorrhœal cast of the uterus. Its walls were from a quarter to one sixth of an inch thick, varying in different parts.

Microscopically the walls of the cast were composed of fibrin enclosing bile pigment, and hexagonal and quadrilateral crystals. The crystals were soluble without effervesence in dilute nitric

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acid, but not in acetic acid. On the outer layer of the cast there were a number of small round-cells, and scattered through the fibrinous network there were a few nuclei. There was no trace of the mucous membrane of the gall-bladder in this membranous cast. No micro-organisms could be seen in specially stained specimens.

Mayo Robson and Macrae, in their description of membranous or croupous cholecystitis, refer to Dr. R. Powell's observations in 1820 to the effect that patients who suffered from what would now be called mucous colitis had attacks of biliary colic followed by jaundice. Cases of biliary colic with membranes in the stools have been observed by Mayo Robson and by Fenwick, and it has been suggested that a condition of the gall-bladder analogous to mucous colitis is present.

In the present case the fibrinous structure of the membrane is quite different from the histological appearance of the intestinal casts of mucous colitis, and the process cannot be considered to be comparable to that of mucous colitis. Its structure suggests a comparison to acute membranous inflammations of mucous surfaces such as have been found to be due to pneumococcal infection, but pneumococci were not found in this case. In one of Mayo Robson's cases of membranous cholecystitis seventy-eight calculi were afterwards removed from the gall-bladder, and in Fenwick's case the patient had almost certainly passed gall-stones previously.

Mayo Robson and Macrae.—'Diseases of the Gall-bladder and Bile-ducts,' p. 32, 2nd edit., 1900.
R. Powell.—'Medical Trans. Royal College of Physicians,' London, 1820.
P. C. Fenwick.—'Brit. Med. Journ.,' 1898, vol. i, p. 1072.

May 20th, 1902.

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40. *"Chyle" cyst of mesentery—intestinal obstruction.*

By JOHN FAWCETT.

H. T—, aged 3 months, was admitted into Guy's Hospital on December 13th, 1902, and died on the next day.

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The patient had been quite well until three days before admission. During the last three weeks he had been fed on "nursery" biscuits, but before that had been fed solely on the breast. Diarrhœa and vomiting commenced on the morning of December 11th and continued. The child when admitted was in an extremely collapsed condition, too ill to do anything in the nature of an operation. She died very shortly.

Post-mortem.—There was an intestinal obstruction caused by a pear-shaped cyst, which was lying partly in the cavity of the pelvis. To the front wall of the cyst a coil of intestine was attached, and the obstruction had been produced by an acute kinking of the coil so attached.

The cyst, which is unilocular, is situated at the intestinal border of the mesentery, a coil of the small intestine being firmly fixed, in fact incorporated, in its wall. It has thus exactly the same characters as those described by Mr. Eve in the 'Medico-Chirurgical Transactions,' vol. lxxxi, 1898. It measures $2\frac{5}{8}$ inches by $1\frac{3}{4}$ inches, and was tightly distended with fluid of a milky character. The wall was thin and smooth. The glands in the neighbouring portion of the mesentery are enlarged, but there is no evidence of their being tuberculous.

Chemical analysis.—Mr. J. H. Ryffel, B.Sc., who kindly undertook the analysis of the fluid for me, reports that "it was milky, containing no lactose or casein, but a trace of a reducing sugar. It contained coagulable proteids, as in 'lymph,' and 7·7 grms. per 100 c.c. of fat. The reaction was alkaline Hence the liquid was chyle, rich in fat."

Microscopical examination.—Several pieces were taken from the wall of the cyst. They are seen to consist of fibrous tissue and unstriped muscle, the latter having no definite arrangement in layers.

Remarks.—The characters of the cyst, of its contents (except for the addition of fat), and the position of it are almost identical with those described by Mr. Eve in the paper above referred to, and those by Moynihan and others. The structure of its wall shows that it arose as a sequestration from the intestine.

Mesenteric cysts have been described under many heads, as serous, chylous, sanguineous, lymphatic, intestinal; but such a classification, based largely upon the contents of the cysts, divides them into a greater number of varieties than seems necessary.

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The contents are to a certain extent a matter of chance, and in view of the comparison of this case with others previously reported, they would, I think, be rightly regarded as arising from embryonic remains. This was suggested by C. Dowd in a very complete paper published in the 'Annals of Surgery,' vol. xxxii, No. 4, 1900.

Thus I think the most satisfactory classification would be to place these cysts under the heading of "embryonic cysts" arising by sequestration from the intestine or its neighbourhood, some from mesoblastic tissue with fibrous and muscular walls, or both; others from hypoblast as well showing epithelial structures.

Since writing the above I have been enabled, through the courtesy of Mr. S. G. Shattock, to incorporate in this note a specimen lately presented to the College of Surgeons by Mr. E. C. Stabb.

"B. 2523. Some of the contents of a thin-walled cyst about two inches in chief diameter which was removed from the outer surface of the small intestine of a child.

"The fluid showed no tendency to coagulate.

"An analysis by Dr. J. B. Leathes proved it to correspond approximately to chyle. The fluid contained 6·23 per cent. of solids and 0·60 per cent. of ash, of which 0·019 was phosphoric acid.

"The ether extract constituted 1·65 per cent., and contained apparently all the phosphoric acid of the fluid.

"This fact and the saponification value of the ether extract (which was high for ordinary fat) made it probable that a certain proportion of the fat was lecithin.

"From a boy aged 6 years, who had been quite well until two months before coming under observation, when there was a history of a sudden attack of abdominal pain and vomiting lasting eighteen hours. He was admitted into the Great Northern Hospital, and discharged as well after seven days. Two similar attacks subsequently occurred, after which laparotomy was performed; nothing was discernible before the operation by the usual methods.

"The cyst was peeled off from the intestine, the free border of which it covered, posteriorly encroaching between the layers of the mesentery." *June 17th*, 1902.

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41. *Aneurysm of the heart.*

By A. F. Voelcker.

On March 27th, 1900, J. D—, a male aged 61, a metal polisher, came under my care in the out-patient department of the Middlesex Hospital. Three days previously while at work he was seized with pain in the right side, which, two hours later, shifted over to the left. On examination there was very little pain or dyspnœa, the radial and brachial arteries were markedly atheromatous, the heart impulse was feeble, and the apex-beat was localised two inches outside the nipple line. The heart-sounds were weak, and there was an occasional systolic sound, which I regarded as a pericardial rub, at the junction of the sixth left rib cartilage and the sternum. No other murmurs were heard. I ventured to diagnose that the patient had a hypertrophied left ventricle, and had probably also an aneurysm of the wall of the left ventricle. Three days later I saw the patient again and found no alteration in the physical conditions, but the pain had disappeared. I urged the patient to come into the hospital, but he would not consent. He was brought in dead three days later.

At the autopsy, which was made by my colleague Dr. Campbell Thomson, the following were the chief changes found:—The body was well nourished. Rigor mortis well marked. The pericardial sac was filled with twelve ounces of blood-clot. The heart was enlarged, chiefly in length, and this was due to the presence of a dark purple-red, subglobular aneurysm, situated on the anterior wall and apex of the left ventricle; the aneurysm was the shape of a tomato, and measured 2½ inches across and 2 inches from above down; the outer surface at the apex was adherent to the parietal layer of the pericardium by firm adhesions. Situated posteriorly at the upper part of the sac was a small rupture; there was a considerable amount of fat on the surface of the heart, and the coronary arteries were felt to be thickened; the heart with the aneurysm weighed 20 ounces; there was no endocarditis of the valves, but the aorta showed well-marked atheromatous changes;

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there was also marked atheroma of the abdominal aorta. The lungs were œdematous. The spleen was enlarged, congested, and weighed 8 ounces. The kidneys were rather fibroid, but not diminished in size. There were some adhesions about the left tunica vaginalis, but there were no positive evidences of syphilis in any of the viscera.

In the 'Transactions' of this Society there are a not inconsiderable number of cases of aneurysm of the heart recorded, and of these the greater number occurred on the left side of the heart, and infinitely more commonly in the ventricle than in the auricle. Of those situated in the left ventricle there are, excluding those in the interventricular septum, records of seventeen cases; of these, one was situated about the middle of the ventricle, ten were at the base, and six at the apex. In my own *post-mortem* experience I have come across three examples of aneurysm of the heart; all have been in elderly males, and in each case the seat has been the apex of the left ventricle. In none of the three cases had rupture taken place.

Aneurysms of the heart appear to arise in one of three ways: (1) from involvement of the endocardium by extension or infection from a valvulitis; (2) from gummatous deposits in the heart muscle; (3) from a myomalacia due to obstruction of a branch of a coronary artery, either from thickening of its walls, with diminution of its calibre, or from the presence of a thrombus or embolus within it.

Aneurysms arising from the first cause are mostly situated towards the base of the heart, or on the interventricular septum. Those arising from the other two causes are either basic or apical, and our 'Transactions' contain excellent examples of both kinds. The three cases I have observed myself were all due to myomalacia arising from partial or complete obliteration of a branch of a coronary artery, and the specimen shown to-night is most probably another example of the same condition.

The pathological excellence of the specimen, and the satisfaction of having diagnosed the condition during life, rather than the rarity of the specimen, must be my excuse for bringing the specimen before the Society to-night.

May 6th, 1902.

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42. *Case of a hat-pin embedded in the heart.*

By H. Campbell Thomson.

The patient from whom the specimen was taken was a female, aged 27, who was admitted into the Middlesex Hospital on August 19th, 1901. Fourteen months before admission she had suffered from an attack of rheumatic fever with pericarditis, for which she was treated at St. George's Hospital.

She had never felt quite well since the attack, but was able to do her work until the end of May, 1901, when she began to suffer from breathlessness and pain in the chest. On admission there was a loud systolic murmur heard at the apex of the heart, and a double murmur (systolic and diastolic) over the aortic area at the base.

The patient gradually became worse, and eventually died September 27th, 1901.

At the *post-mortem* examination the heart was found to weigh sixteen ounces; the pericardium was universally adherent, but could, with some difficulty, be separated. The heart muscle had undergone extensive degeneration.

A hat-pin—without the head—two and a half inches in length, was found embedded in the wall of the right ventricle immediately below the pulmonary valves; the point of the pin passed through the wall of the aorta just above the aortic valves, and projected into the lumen of the aorta, reaching about halfway across. The point of the pin was covered with blood-clot, some of which was calcified, and from this fact, and the firmness with which the pin was embedded in the heart muscle, it was evident that it had been there for some long time. Although the pin only passed through about half the diameter of the aorta, its point had evidently, at some time or other, impinged against the opposite wall, as seen by a localised injury to the aorta opposite the point of the foreign body.

There was no evidence to show when or how the pin got there. Through the kindness of Mr. S. G. Shattock I am able to mention a somewhat similar case, the specimen of which is preserved in the museum of the Royal College of Surgeons [B. 2933].

The patient in this case was a man about thirty years of age who died from acute uræmia. After death a needle was found

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in the wall of the left ventricle; it projected directly into the ventricular cavity for three fifths of an inch. The external site of perforation was one inch and a quarter from the interventricular groove, and the same distance from the auriculo-ventricular. The portion of pericardium corresponding with the site of perforation presented a discoid thickening about a third of an inch in diameter. From the position of the perforation it was thought probable that the foreign body reached the heart from the lower end of the œsophagus. *May 6th*, 1902.

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43. *On a microbe obtained from the dead rat, and resembling the* Bacillus pestis.

By E. Klein.

To show the difficulties sometimes connected with the diagnosis of plague in rats, and also to emphasise the importance—in the bacterioscopic analysis of material suspected to be that of plague—of submitting such material to all and every test required for safe diagnosis, the following instance is a good illustration.

A dead rat was forwarded for bacterioscopic analysis. This rat was found with a number of other dead rats amongst the cargo in a steamer which arrived in Bristol from a country known to be infected with plague. From the lung of the rat a microbe was isolated by culture and by animal experiment, which (*a*) in morphological respects,—size, bipolar staining, not staining by Gram, non-motile; (*b*) in respect of causing bubo and hæmorrhagic swelling at the seat of inoculation, with enlarged spleen, both in guinea-pigs and rats, resembles the *Bacillus pestis* in so remarkable a manner (demonstration of lantern slides) that it would be quite impossible for anyone to declare from these results that we were not dealing with plague; and yet the culture characters prove conclusively that the microbe is certainly not *Bacillus pestis*, but one having broad characters in common with *Bacterium lactis aërogenes*, while in other respects it possesses those of *Bacillus coli communis*.

The appearance of the colonies in plates, the streak and stab culture in gelatine, the appearance on potato, are exactly like

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those of *B. lactis aërogenes;* while the production of gas bubbles in shake culture, the production of indol in broth culture, the formation of acid, the curdling of milk, and the positive action in neutral red are exactly like those of *B. coli communis.*

May 6th, 1902.

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44. *The meningococcus in a case of cerebral tubercle simulating posterior basic meningitis.*

By Clive Riviere.

The case from which this specimen was obtained occurred in the Shadwell Children's Hospital, under the care of Dr. Dawson Williams, to whom I am indebted for permission to publish the ward notes. Clinically the case was one of progressive hydrocephalus coming on in a child of 9 months. The symptoms resembled those of posterior basic meningitis, and a diagnosis of that disease was made and seemed to be confirmed or, at any rate, upheld by the presence of the meningococcus in the ventricular fluid drawn off to relieve intra-cranial pressure. At the *post-mortem* examination no meningitis was found, the hydrocephalus being due to obstruction of the Sylvian aqueduct from pressure of a large caseous mass. The points of interest in the case are the growth of the meningococcus in the pent-up cerebro-spinal fluid, and the very unusual size of the caseous tumours in the brain.

The notes of the case are as follows:—A male child aged 9 months was admitted on December 16th, 1901, with a history of head retraction of four weeks' duration. For two weeks the arms and legs had been stiff. There had been no convulsions, no vomiting. Cough had been present for several months past.

Family history.—The mother died of phthisis seven weeks after the birth of the child.

History of present condition.—A pale, poorly nourished child. Head markedly retracted, neck stiff. Anterior fontanelle large, bulging, and tense. The lower half of the face on the right side was completely paralysed; the forehead and right eyelid moved normally. There was ptosis on the left side, and occasional

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strabismus, sometimes of one eye, sometimes of both. The pupils were equal, of medium size, and reacted to light. The arms were held flexed at the elbow, and there was some rigidity, but no tendon reflexes were obtainable. The legs were kept partially flexed at hip and knee joints, and were slightly stiff. The knee-jerks were much exaggerated, and ankle-clonus was obtainable on both sides. The heart was natural. In the lungs a few râles were heard at the bases behind. The abdomen was natural.

A few weeks later the child was noticed to be blind, the intra-cranial pressure and the rigidity of the limbs continued, and the child began to waste. Five weeks after admission the head was retracted to the right side with the face turned to the right, the body was bent to the right, and there was increased rigidity of the right leg. As the head was increasing in size, having a circumference of $17\frac{1}{2}$ inches on February 20th (about nine weeks after admission), on February 24th an exploring needle was passed through the anterior fontanelle into one of the lateral ventricles and 1 oz. of fluid withdrawn, after which it was allowed to leak for three days. A week later it was noted that the head retraction and facial paralysis had entirely disappeared. The right leg was kept drawn up, but there was never any paralysis of the limbs. To relieve the recurring intra-cranial pressure the brain was further tapped three times, 1 oz. of fluid being withdrawn, and leakage allowed on each occasion. The progressive wasting and the hydrocephalus continued, and the child died on March 27th, after an illness of four and a half months. The temperature was irregular throughout, often rising to 100°, but seldom higher. There was diarrhœa during the first two months, but none latterly.

A diagnosis of posterior basic meningitis was made. A *post-mortem* examination on March 29th showed the following appearances:

Post-mortem.—The body was extremely emaciated. There were caseous glands in the neck, and in the thorax the bronchial, tracheal, and bifurcation glands were enlarged and caseous, but none softened. The lungs contained racemose collections of tubercles, a few "caseous blocks," and there was early caseous consolidation of the lower lobe of the left lung. Besides these changes there was a limited general tuberculosis,

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most of the other organs containing a few tubercles. The examination of the head I will describe in more detail. There was very marked hydrocephalus, more than I have ever seen in a case of posterior basic meningitis, however chronic. The sutures were widely separate, and the fontanelle bulging. On removing the back of the skull-cap and the upper cervical vertebræ, the cerebellum, posterior subarachnoid space, and the cord were found perfectly healthy, and there was no accumulation of cerebro-spinal fluid in this region. The brain being removed, enormous distension of the ventricular system and great flattening of the surface convolutions was apparent. After hardening in formalin vertical transverse sections were made at different levels, and drawings from three of these serve to illustrate some of the following points.

The tumours.—In the *left* hemisphere lies a firm, yellow, caseous mass, measuring 1½ inches from before backwards, 1½ inches from side to side at its widest point near the middle of the crus, and ⅞ inch from above downwards. It is situated in the basal nuclei, and extends from the optic chiasma backwards to behind the middle of the pons, stretching the parts in which it grows, so that the dimensions of their surface are increased. It replaces and obliterates the optic thalamus, posterior limb of the internal capsule, and lenticular nucleus on that side, fills the left crus where it reaches the surface below, presses on and displaces the right crus, and passes backwards into the pons, stretching out the transverse fibres which pass over it, and displacing and closing the Sylvian aqueduct. The anterior limb of the internal capsule and the head of the caudate nucleus escape as they lie in front of the growth, and the tail of the latter is flattened out as it passes over it.

In the *right* corpus striatum is a similar but smaller caseous mass. It is nearly spherical, with a diameter of three quarters of an inch, is placed in the optic thalamus, and presses on the posterior limb of the internal capsule and the lenticular nucleus which lie below and external to it. The head of the caudate nucleus is anterior to it, but the tail is flattened as it runs over it. It does not involve the crus, which is interfered with, however, by the growth of the opposite side.

Besides these two masses there is an irregular nodule of about three quarters of an inch in diameter at the junction of the

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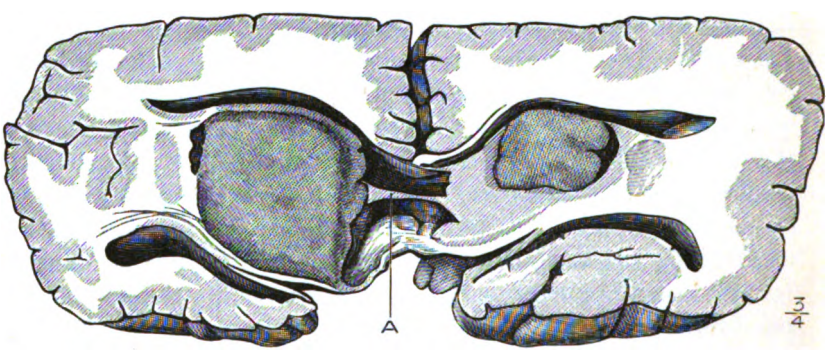
mesial and upper surface of the *right* hemisphere near the upper limit of the ascending frontal convolution, and a smaller nodule in the *left* frontal lobe on its orbital surface.

Owing to the closure of the aqueduct of Sylvius the ventricular system is enormously dilated with clear fluid, and its walls correspondingly stretched and thinned out.

It is remarkable that, in spite of the marked involvement of the motor fibres, there was at no time any paralysis of the limbs.

As was mentioned in the notes, fluid was withdrawn from the ventricles during life on four occasions to relieve intracranial tension, and from the first two specimens cultures were

FIG. 29.



Section 1.—Posterior view of vertical transverse section through brain at level of tuber cinereum, showing the caseous masses in the corpora striata and the great dilatation of the lateral and third ventricles. A. Soft commissure.

taken. The fluid was quite clear, like water, and there was no cellular deposit.

From the first supply on February 24th a diplococcus was obtained in pure culture. From the second supply on March 12th a diplococcus of similar morphological and cultural characteristics was obtained, also in pure culture, and in the fluid after death a diplococcus was also found, and associated with it a bacillus whose characteristics I will describe later. These results were confirmed by examination of films made from ependymal scrapings.

Diplococcus.—The diplococcus is gonococcus-shaped, and appears to possess a capsule, stains readily with methylene blue, and retains Gram's stain unevenly, most staining well, but

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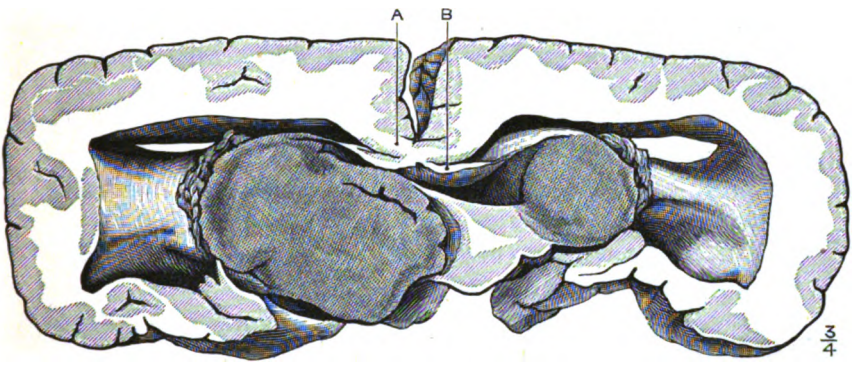
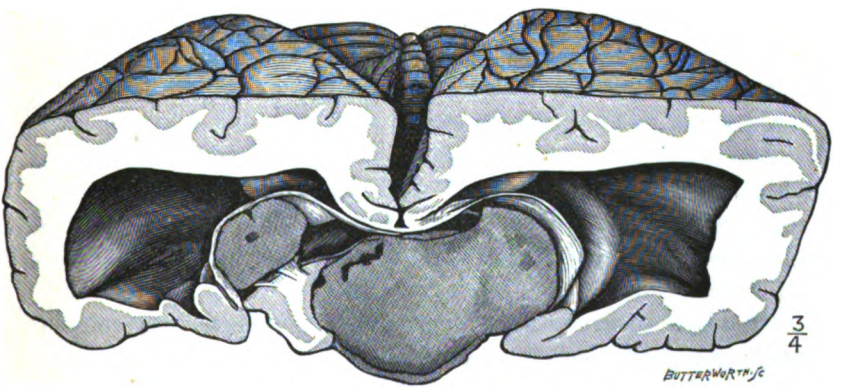
some individuals decolourising. They are arranged in couplets or in groups of four, which, in films made from agar cultures,

FIG. 30.



Section 2.—Posterior view of vertical transverse section through middle of crura cerebri, showing caseous tumours and dilated ventricles. The thinning out of the brain substance round them and the flattening of the convolutions are well seen. A. Corpus call. B. Fornix.

FIG. 31.



Section 3.—Section through same level as last, showing posterior portion of brain. The left crus is obliterated by the large caseous mass; the right crus is free but displaced. The opening of the aqueduct of Sylvius is also displaced and closed. The dilated posterior horns of the lateral ventricles and a pouching of the third ventricle towards the great transverse fissure are well seen.

tend to cling together, giving to casual observation a resemblance to staphylococcus.

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As there are some differences between the cultural characters of the first two specimens and the last, it will be convenient to describe the first two together and the last separately. Cultures obtained on February 24th and March 12th showed the following characters:

On *agar*.—Minute greyish-white, rather dry-looking colonies; growth by no means luxuriant.

On *serum*.—Good growth of large flat colonies; nearly invisible on the background of the serum.

On *gelatine*.—Good growth of isolated greyish-white button-like colonies; no liquefaction.

In *broth*.—Considerable turbidity after twenty-four hours, with a fair amount of deposit readily shaken up.

In *litmus milk*.—Acidity after twenty-four hours; no clotting subsequently.

The *diplococcus* obtained from the ventricular fluid after death was identical morphologically, but showed some cultural differences.

On *agar*.—The colonies were greyish-white, shining, raised, and button-like, running together into a thick grey film.

On *gelatine*.—A very fine, dry, feathery growth.

In *broth*.—After twenty-four hours very slight cloudiness, and a floccular precipitate not readily broken up by shaking.

In *milk*.—Remains neutral; no clotting.

On *potato*.—No visible growth.

Bacillus.—The *bacillus* obtained from the fluid after death I have been unable to identify. It is fine, thread-like, with some segregation of protoplasm, stains poorly with ordinary dyes, and does not hold Gram's stain. It is fairly actively motile, and shows no spores.

On *agar*.—It grows somewhat slowly, as minute grey colonies running together into a greyish film.

On *serum*.—It grows much more readily as an abundant yellow, lustrous smear.

On *gelatine*.—No visible growth after twenty-four hours; in three days a slight film of minute colonies which show distinctly yellow when larger. After one week marked liquefaction is seen.

In *broth*.—Slight cloudiness in twenty-four hours; no deposit; in one week turbidity with much deposit.

In *milk*.—No acidity or clotting, but after one week it is

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digested to semi-translucent beer-coloured liquid, with no putrid odour.

On *potato*.—After many days growth of brown-yellow shining colonies.

Conclusions.—The diplococcus obtained from the cerebro-spinal fluid does not conform rigidly in its cultural characters to either of the two well-recognised varieties of the meningococcus. These varieties have been designated by Pfaundler (1), after those who first described them, the type of Weichselbaum and the type of Heubner.

The organism belonging to the first type, that described by Weichselbaum, grows on agar and serum as semi-transparent grey colonies; there is little or no growth on gelatine, broth, or milk. The organism has little vitality, and generally dies in a few days. Gram's stain is nearly always negative.

The organism belonging to the second type, that of Heubner, is much more active on culture media. It forms abundant growth of glistening white colonies on agar and serum, grows well in broth, and fairly well as a rule on gelatine and in milk. Its viability is measured in months, and it stains well by Gram's method.

Among eight cases of posterior basic meningitis occurring lately, in which I have been able to isolate the organism, in one it conformed to the first type, in five to the second type, and in two cases both varieties were found either together, or separately in fluid obtained on different occasions.

In all these cases one or other type was followed fairly closely, but Pfaundler recognised varieties lying between these two and uniting them into a common group, and the diplococcus I have described seems to me to belong to this intermediate category. By what means it found its way into the pent-up cerebro-spinal fluid it is difficult to decide; the entrance from the nose to the meninges in cases of posterior basic meningitis appears to be by no means problematical, but the road into a plugged ventricle, unless by the blood-stream, is far to seek.

The presence of the meningococcus in cases of tubercular meningitis has been demonstrated in a fair number of instances. Huebner (2), Lenharz (3), and Netter (4) each describe two examples of this condition. In these cases, no doubt, the organism was responsible for some part of the inflammatory

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process, but in the case just described it seems to have found the pent-up fluid a convenient medium for its growth, and to have added thereby little or nothing to the pathological conditions already present.

I have been unable to find any cases recorded in which the organism was found under these conditions, and for this reason the present case seemed worthy of publication.

1. *Pfaundler.*—'Jahrbuch für Kinderheilkunde,' 1899, xlix, p. 264.
2. *Huebner.*—'Deut. medic. Wochenschr.,' 1897.
3. *Lenhartz.*—XV Congress für innere Medicin, Berlin.
4. *Netter.*—'Twentieth Cent. Pract. Med.'

January 17th, 1902.

45. *Fibro-sarcoma of the pancreas in a child.*

By J. D. Malcolm.

The patient was four years of age. Her father and mother are both alive and well, and they have one other child, a healthy girl, born in 1897. One of her grandfathers was said to have died of an internal cancer at the age of sixty-five. Whilst the patient was under immediate observation the bowels were very constipated. There was no albumen in the urine, which was scanty (sometimes only twelve ounces in twenty-four hours) and deposited urates, its specific gravity being usually about 1030.

An abdominal swelling was first noticed in April, 1898. In May, 1898, I found an obvious swelling in the upper part of the left side of the abdomen. It was firmly held in the position of a renal tumour, but the attachments seemed sufficiently lax to allow of the growth being shelled out of its bed. The patient was, however, extremely emaciated and anæmic, and operation was for this reason deferred.

In October, 1898, she had improved very much in her general condition, but the tumour had increased in size, though not to any great extent. It distended the hollow of the left loin, pushing the lower ribs upwards and forwards, bulging the side outwards, extending across the abdomen as far as the outer edge

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of the right rectus muscle, and downwards to below the level of the anterior superior iliac spines. The greatest girth of the body was 23¾ inches a little above the level of the umbilicus. On palpation the mass was smooth and elastic. It could be grasped between a hand in front of the abdomen and the other hand behind the loin, and, although it was firmly held, there was still a slight mobility of the tumour, sufficient to make me think that I could remove it. There were some easily felt glands in both axillæ and in both groins, but they were not enlarged, and the veins over the upper part of the abdomen were distended. No disease of the heart or lungs was detected.

On November 4th, 1898, I opened the abdomen through the upper part of the left linea semilunaris, and exposed the tumour with the splenic flexure and adjacent portions of the colon fixed in front of it. The most convenient place to open the retro-peritoneal space in which the tumour lay was above the transverse colon, and when the peritoneum in that situation was divided I had no difficulty in separating the tumour from the connective tissue in which it was loosely embedded. Some firm adhesions to the lower end of the spleen were separated, and the new growth was then easily withdrawn from the abdominal cavity, the tail of the pancreas being dragged out with it. The tumour was then only attached to the pancreas, and it was impossible to separate the two without cutting through pancreatic tissue. In doing this large vessels were divided, but the hæmorrhage was easily controlled by ligature. No ureter was seen during the operation.

There was a second new growth about the size of a bantam's egg to the right of the cavity from which the tumour had been removed. I thought that this was a collection of glands affected by malignant disease, but the patient was in such a serious state of collapse that it was out of the question to attempt an investigation of the nature and connections of this second abnormal condition. I therefore ligatured all bleeding points, having much trouble in securing those on the spleen. I washed out the abdominal cavity with warm sterilised salt and water, leaving as much as possible inside, when the wound was sewn up, with a view to counteracting the shock of the operation, which, however, was not survived by the patient.

At the autopsy, caseating glands were found near the bifur-

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cation of the bronchi, and in the anterior mediastinum. There were extensive old pleuritic adhesions on the right side. There was no sign of peritonitis. The peritoneal cavity was full of fluid (the salt and water introduced at the operation), which at first flowed away clear, but that from the loin pouches was deeply blood-stained. The kidneys were normal. Part of the transverse colon was separated from its attachments, its mesocolon having been completely divided; and the omentum had been removed from all but the left one and a half inches of the stomach. The left pleuro-colic fold was intact. The spleen had a wound in the lower end of its inner surface one and a half inches long. The left half of the pancreas was absent, its cut surface presenting many ligatured points.

There was a smooth encapsuled growth situated in the gastro-hepatic omentum, with the bile-duct and some vessels in front of it. The colic impression on the liver, the neck of the gall-bladder, and the transverse fissure of the liver were above it. The foramen of Winslow was behind, and the new growth seemed to be connected with the head of the pancreas below, the connection between the two being much constricted.

The parts were sent to the Royal College of Surgeons. On dissection the mass in the lesser omentum was found to be a new growth lying within the portal vein, and distending it. The preparation' (No. 2836 B) shows the liver and the divided portal vein. In dividing the vein the tumour was cut in two, the larger of the parts being quite unattached; the lesser was attached only by portions of its circumference, so that a probe could be passed along the lumen of the vessel.

Mr. Shattock found the tumour of the pancreas and that within the portal vein to be fibro-sarcomata.

Although the nature of the tumour removed in this case was doubtful even at the end of the operation, the conditions found at the *post-mortem* examination showed that it certainly had grown from the pancreas, from which it had been noted that the chief blood-supply of the new growth came. A larger portion of this organ had been removed than I thought when operating. The differential diagnosis between an enlarged kidney and a tumour of the tail of the pancreas may be quite impossible. Once before[1] I operated on a tumour having almost

[1] 'Med. Soc. Trans.,' 1898.

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exactly the same relations as in this case to the tail of the pancreas and to the surrounding structures; the tumour was mistaken for a renal enlargement not only by myself, but by three of the most experienced men in London. I removed in that case a cystic tumour, having to divide the pancreatic tissue as in the case now recorded. During the operation the kidneys and spleen were found to be in their normal positions. The patient made a good recovery and is still alive.

February 18th, 1902.

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46. *Neuro-lipomatosis.*

By H. J. Waring.

The patient from whom the specimen was obtained was a man aged 38, who gave the following history of the onset of his disease. He was quite well until June, 1895, when his right forearm and hand were crushed by a heavy bar of wood. No bones were broken, but as a result of the injury the patient was unable to follow his usual occupation for a period of fifteen months. In June, 1896 (one year after the occurrence of the injury), the patient suffered from severe pains in the right hand and stiffness in the right thumb and forefinger. From this date until October, 1900, the changes which were now apparent in the conformation of the limb gradually developed. On one occasion an exploratory incision was made into the soft tissues of the swollen thumb, but according to the statement of the patient no fluid was evacuated. From October, 1900, until April, 1901, when the patient first came under observation, enlargement of the right thumb and forefinger took place rapidly; a swelling appeared in the soft tissues immediately above and on the inner side of the right elbow, whilst attacks of increasingly severe pain occurred along the course of the arm and on the anterior margin of the trapezius muscle on the right side. From the statements made by the patient, these attacks of pain appeared to involve chiefly the median nerve and the region of the brachial plexus. When first seen in April, 1901,

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the radial side of the right hand and forearm presented the appearances shown in the cast exhibited. The right forefinger and thumb were considerably enlarged and apparently elongated. The extremity of the forefinger was bent upon itself almost at a right angle, so as to lie on the palmar aspect of the distal portions of the middle and ring fingers. Movements in the metacarpo-phalangeal joints were present, but in the interphalangeal joints they were entirely absent. A soft non-fluctuating swelling occupied the thenar eminence and the radial side of the palm, and extended upwards two inches above the level of the wrist. A hard swelling could also be felt in the substance of the biceps muscle a little above the elbow. Attacks of severe pain in the hand and forearm and in the lower part of the right side of the neck kept the patient awake at night. All the electrical reactions were normal, with the exception of those of the abductor pollicis, in which none could be obtained. The region of the palmar swelling and the palmar aspect of the affected digits were very tender on pressure. Owing to the difficulty in reaching an exact diagnosis, an exploratory incision was made into the swelling in the biceps muscle. This was found to consist of hard fibrous tissue, probably the remains of a former injury. On account of the attacks of severe pain and the comparative uselessness of the limb, an amputation was performed through the forearm above the level of the swelling. The median nerve was found to be thickened, and had to be drawn downwards in order to make the section through sound tissue. On dissection of the amputated portion of the limb, the enlargement on the palmar aspect of the forefinger and thumb, the radial side of the palm, and lower part of the forearm was found to be due to a tumour which occupied the course of the median nerve. The tumour was composed almost entirely of fat, and appeared to consist of two parts—(*a*) a lipoma around but outside the sheath of the trunk of the median nerve and its branches to the thumb and forefinger, and (*b*) a growth of fatty tissue between the individual bundles of nerve-fibres within the main nerve-sheath. In the thumb the branches of the median nerve were enormously thickened by fatty and fibrous tissue. On the radial side of the index finger and the distal portion of the ulnar side of the same digit a similar thickening was apparent in the nerve branches. A skiagraph revealed con-

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siderable enlargement of the phalanges, and obliteration of the interphalangeal joints. On histological investigation the median nerve and its branches were found to have a large amount of fatty tissue within the nerve-sheath, but the nerve-fibres did not appear to have undergone any marked change. No changes were noted in the radial and ulnar arteries. The specimen is an example of a very unusual pathological condition. The injury received in 1895 appears to have been the starting-point in the development of the lipomatous tumour around and in the median nerve and certain of its branches. The hypertrophy of the phalanges, and the consequent production of the curious deformity of the index finger, may be due to altered nervous influences upon the nutrition of the part. *June 17th*, 1902.

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47. *Syphilitic patch on pharynx showing hyaline fragmented bodies.*

By Norman Dalton.

The specimens are taken from a man aged 36 years, who died of phlegmonous inflammation of the fauces and œdema of the larynx. There were pigmented syphilitic scars on the legs.

One or two white patches were found on the pharynx. They looked like those seen on the tongue in syphilis, but on microscopical examination they showed intense acute inflammation. Remains of the mucous membrane could be seen, but the submucous tissue, muscle, and glands were thickly infiltrated with necrotic leucocytes. A noticeable point was that there was much fibrin round the vessels in the submucous tissue. The epithelial cells of the glands were swollen as in catarrhal conditions.

In the connective tissue round the gland acini numerous hyaline bodies were seen. They were not found at any distance from the glands, and in sections which contained no glands none were found. In several places the bodies could be seen to have invaded the gland acini, lying just within the basement membrane, between the columnar epithelial cells, and

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in one case apparently free in the lumen of an acinus. Those which lay between the epithelial cells pushed the latter apart, so that they lay in a clear space—an appearance which was rather suggestive of a parasite. But I may say here that I do not think that they are parasites.

The bodies are hyaline, and many of them when examined under a $\frac{1}{6}$ objective can be seen to have broken up into roundish or slightly angular fragments. Under the same power many of them appear to be nucleated. Under a $\frac{1}{12}$ it seems that the nucleus either does not belong to the cell, or that it is quite at the periphery. Two or three of our most expert microscopists have seen these sections, and they think that the bodies are not nucleated. But I rather think that the nuclei are connected with the bodies, even if they be almost extruded from them; because some of the bodies which are apparently nucleated stand apart from other cells (the nuclei of which might appear to belong to them), and even under the highest magnification no other cell body to which an overlying nucleus could belong can be made out. I think, therefore, that the nucleus is pushed out by the swelling of the degenerated protoplasm, and I feel rather strengthened in this opinion by the fact that Unna has described similar bodies which he distinctly says are nucleated. The presence of the bodies outside and inside the glands suggests that they were at one time amœboid, and that some have undergone this hyaline degeneration after they have penetrated the basement membrane.

I think that they must be connective-tissue corpuscles which have undergone hyaline degeneration, because they must have been amœboid, and conceding that the nuclei belong to them, many of these nuclei are oval and clear, with a few granules. The fact that the bodies are hyaline, and tend to break into fragments, suggests that the degeneration is like that of Zenker, particularly as the surrounding inflammation is partly fibrinous. In diphtheritic inflammation of the arches of the palate I have found Zenker's degeneration in the underlying muscle.

The bodies stain deeply with eosin, but with the Ehrlich-Biondi they take up the orange, not the fuchsin. They do not stain with the picro-carmine solution I use as a counter-stain to logwood.

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I have looked for syphilitic lesions in similar situations since I met with this case about four years ago, but I have only come across one, in a woman who died of ulcerative colitis, whose skin showed numerous syphilides. The vagina was inflamed and ulcerated, and I found two hyaline bodies close to each other in a deep part of its submucous connective tissue. It is noticeable that these do not lie near any mucous gland.

I mentioned that Unna has described similar bodies in the lesions of actinomycosis, and through the kindness of my colleague, Dr. Whitfield, I am able to show a section in which these bodies are conspicuous. Unna says that they are degenerated plasma cells, the protoplasm of which, as degeneration progresses, ceases to be basophile and takes the acid fuchsin deeply. On reading Unna's description in his histopathology of skin diseases, it seems clear that the hyaline bodies seen in my cases are the same as those he describes. In his cases it is clear that there was nothing like an aggregation of the bodies round the mucous glands, such as is seen in my pharyngeal case, but not in the vaginal one. As I have not employed his stain, I cannot tell whether the pieces of broken-up cell would stain so deeply as is seen in Dr. Whitfield's section. Further, judging from Unna's coloured plate, the nucleus of the hyaline cell is a much more conspicuous object than in any of my specimens. These may be minor differences, but in most respects the bodies agree. Unna thinks that the degeneration is due to the toxins produced by actinomyces. It is not possible to say whether in my case the toxin is that of syphilis or of some bacterium which has produced a secondary infection. From the apparent rarity of these bodies the cause is probably syphilis, and to judge from my two cases, the best place to look for them is a mucous membrane not far from the skin.

It is noteworthy that what Russell thought to be "fuchsin bodies" of the same nature as those described by him in carcinoma, were found by that observer in two specimens of syphilitic lesion.[1] *February 4th*, 1902.

[1] 'British Medical Journal,' Dec. 13th, 1890.

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48. *A case of tuberculosis in the sheep.*

By Alexander G. R. Foulerton.

The rarity of tuberculosis in the sheep is shown by the fact that so good an authority as Professor John McFadyean, of the Royal Veterinary College, when reporting such a case less than two years ago, was able to say that it was the first indubitable example of the occurrence which had been recorded in this country.

The specimens which I show this evening came from the carcass of a sheep which had been seized as tuberculous in Smithfield Meat Market on January 30th, 1902, by Dr. George Newman, medical officer of health to the borough of Finsbury; and my best thanks are due to Dr. Newman for his very kind permission allowing me to show the case here. Dr. Newman's note of the condition of the carcass states that it was that of a half-bred ewe and was extremely emaciated, weighing only about 35 pounds instead of about 65 pounds as the carcass of a healthy ewe of the same measurement would weigh. The flesh was pale in colour, and soft and flabby; the tissues generally were œdematous. Both lungs were extensively consolidated, and contained numerous tubercles; and there were also numerous tubercles, varying in size from that of a pin's head to that of a pea, on the pleuræ of both sides. There were tubercles in the liver, spleen, and both kidneys. The right inguinal glands, which contained caseating areas, formed a mass the size of a hen's egg. The anterior mediastinal, sternal, cervical, mesenteric, lumbar, and dorsal glands were enlarged, and contained caseating patches.

The specimens now shown are portions of one lung, the liver, a kidney, mediastinal glands, and a portion of the neck showing some enlarged cervical glands.

In different places the nodules have undergone either a caseous or a calcareous degeneration. The calcareous degeneration is especially in evidence in the cervical glands and in the liver, the latter containing a large number of small calcareous nodules.

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A number of smear preparations made from the lymphatic glands failed to show the presence of any acid-fast bacilli, but the nature of the case was proved by the results of guinea-pig inoculation.

Four guinea-pigs were inoculated with an emulsion made from one of the mediastinal glands; two received the emulsion as it was, the other two after it had been heated at 60° C. for ten minutes. The animals were inoculated in the popliteal space, and the two which received the unheated emulsion died within seventy-two hours with a septic infection. Of the two remaining guinea-pigs which received the heated emulsion, one died twenty-eight days after inoculation with a tuberculosis of the popliteal, inguinal, and lumbar glands, and the other one died thirty-five days after inoculation with a more general infection. The lesions in both animals showed a large number of acid-fast bacilli.

The virulence of the strain of bacillus present seemed to be much the same for the guinea-pig as that of one isolated from a human source, so far as could be judged from the results of only two experiments. A further series of guinea-pigs have been inoculated from the infected glands of the first two, in order to test this point; but the results of this second set of experiments are not yet available.

Whilst the rarity of tuberculosis in sheep in this country is undoubted, the records of slaughterhouses on the Continent would make it appear that in some countries it is a little more common. Nocard quotes the record of the Prussian slaughterhouses for 1895–6 as giving the proportion of tubercular sheep and goats, taken together, as 1 in 1000; in the Saxony slaughterhouses during 1896 the proportion of tubercular sheep and goats was 7 in 10,000; and in the Moscow slaughterhouses in 1893 the proportion of tubercular sheep alone was 1 in 5000.

But these statistics are of little value as an indication of the prevalence of tuberculosis in sheep, since the methods of slaughterhouse inspection do not discriminate with any degree of accuracy between a tuberculosis caused by Koch's bacillus and certain other morbid conditions which closely simulate it in the naked-eye appearance of the lesions produced—such as the ill-named "pseudo-tuberculosis" of sheep described by Preisz and Guinard, by Guinard and Morey, and by Turski. Cherry

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and Bull[1] have also described a disease, similar to the last, observed amongst sheep in the Melbourne slaughterhouses, due to a bacillus, and manifested by an enlargement and caseation of the lymphatic glands. The rare occurrence of tuberculosis in sheep is not the result of a natural immunity; for the animal may be experimentally infected without any difficulty, either by inoculation or by feeding. And the case which I have shown proves that the animal is highly susceptible to a natural infection.

This rarity of tuberculosis in the sheep contrasts strongly with the excessive prevalence of the same disease in certain classes of cattle, and is probably explicable by the habit of life of the sheep.

The incidence of tuberculosis amongst different classes of cattle appears to be principally determined by the conditions under which they live. The disease is most common in dairy cattle which are crowded together in confined byres, without adequate means of ventilation — the proportion of infected cattle in different herds kept under these conditions being anything between 20 and 90 per cent. Amongst the Aberdeenshire cattle, for instance, which live almost entirely in the open air, tuberculosis is, on the other hand, extremely rare. And it is almost certainly to their open-air habit of life that sheep owe their freedom from tuberculosis. *January 15th*, 1902.

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49. *Tuberculosis of the œsophagus in a python.*

By S. G. Shattock.

The following specimen may be worthy of record, partly on account of the unusual site of the disease—the œsophagus,—partly because spontaneous tuberculosis in "cold-blooded" forms is rare, and has a certain interest from the biological side of the tubercle bacillus itself.

[1] Cherry and Bull, "Caseous Lymphatic Glands (Pseudo-tuberculosis) in Sheep," 'Intercolonial Medical Journal of Australasia,' May 20th, 1899.

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The python (*Python molurus;* India), a female measuring fifteen feet in length, was sent to the Royal College of Surgeons from the Zoological Society's Gardens, where it died after having been ill for about two months.

The tubercular lesions, so far as they were recognisable by the naked eye, were confined to the stomach, œsophagus, and lungs: the pericardium was the seat of recent acute inflammation, probably due to septic infection arising at the seat of the main tubercular lesion of the stomach, which was deeply excavated.

As regards the lung, from the walls of the alveoli there project a certain number of small spherical tubercles, and many are discernible in the deeper part of the pulmonary tissue in the cut edge of the specimen; some have undergone calcification; groups of minute tubercles are visible, moreover, on the external surface of the organ.

In the human subject tuberculosis of the œsophagus is almost unknown, except as consequent on disease of some contiguous structure, as the vertebræ. Like the trachea, the œsophagus may be perforated by suppuration occurring in connection with caseous lymphatic glands, bronchial or mediastinal. The perforation may be single or multiple. A good example of the latter is recorded by Dr. G. N. Pitt in vol. xxxix of the Society's 'Transactions;' in this case (of a woman æt. 67 years) there were six groups of perforations related to tubercular lymphatic glands along the œsophagus, the pus from each having burrowed through one or more openings with sharply defined edges; the sixth and seventh cervical vertebræ were the seats of suppurative caries, and the bronchial and cervical glands were caseous from tubercular disease. No pulmonary lesion is mentioned as having been present.

In the Brompton Hospital Museum there is a preparation (L 219) which was exhibited and catalogued in the collection shown at the British Congress on Tuberculosis (London, 1901) as one of multiple tubercular ulceration, but an examination of the lesions has since shown such an utter want of histological evidence that the specimen can no longer be retained in the category of tubercular disease. There is, however, a second, (O 100) lately added to the same museum, which is a true example of this very rare condition. The upper end of the

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piece preserved (which comprises the middle and lower parts of the œsophagus) exhibits many small ulcers, some of which have coalesced, and reach the muscular coat. The microscopic sections show a somewhat diffuse lesion of the mucosa and submucous tissue, the inflammatory formation containing typical caseating foci and groups of giant-cells. Tubercle bacilli were found in scrapings from the ulcerated surface. The parts came from a man æt. 54 (under the care of Dr. T. D. Acland),[2] an upholsterer, who died of chronic pulmonary tuberculosis. After death the stomach was found extremely contracted, but apparently normal. The lower part of the ileum, the cæcum, and the whole of the large intestine as far as the sigmoid were extensively ulcerated; and besides the pulmonary disease (old and progressing) there was left pyo-pneumothorax, and ulceration of the trachea; the cervical lymphatic glands were normal; the bronchial, mediastinal, and mesenteric were enlarged. Examination of the larynx, pharynx, and higher part of the œsophagus was not permitted.

The rarity of such lesions appears from the fact that in the article by Zenker and Ziemssen on "Diseases of the Œsophagus" ('Ziemssen's Cyclopædia,' 1878) the occurrence of œsophageal tuberculosis is regarded as an open question, the three examples till then recorded as such having been unaccompanied by microscopic examination.[1]

Simultaneously with the publication of the above article, however, an unusual and interesting case of true œsophageal disease was recorded by Breus ('Wien. med. Woch.,' 1878, p. 258). It concerned a man, the subject of phthisis, who attempted suicide by drinking caustic potash; death took place about four months afterwards. At the autopsy, besides the chronic pulmonary tuberculosis, there were found tubercular ulcers of the small and large intestine, and recent tuberculosis of the liver, spleen, and kidneys. Here, besides tubercular ulceration of the pharynx and stomach, there was extensive disease of the œsophagus, the tubercular character of which was proved by histological examination. The author concludes by stating his view that the inflammatory process set up by the corrosive had, in this tubercular subject, taken on a specific

[1] Paulicki ('Virchow's Archiv,' Bd. xliv, p. 373), Chvostek, and Kraus (quoted by Birch-Hirschfeld).

[2] To whom I am indebted for permission to refer incidentally to the case.

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character. The tubercle bacillus was not then discovered. At the present time we should regard the œsophageal tuberculosis as due to sputum inoculation of the surface resulting from the separation of the slough.

In his monograph ('Beiträge zur Lehre von der Tuberculose,' Marburg, 1882) E. Frerichs has analysed 30 carefully observed cases of acute, and 250 of chronic tuberculosis, with the following results:—In none of the acute was the œsophagus involved. In the chronic the œsophagus was found tubercular in one (a child). The lesions consisted (*a*) of multiple sharply defined ulcers, the floor of which presented caseous *débris*, and (*b*) of obvious nodules in the intact mucosa. The intestinal tract was beset with numerous ulcers, which began in the pharynx, and after skipping the stomach, appeared again in the upper part of the small intestine, reaching onwards to the colon. In this case, as in that by Breus, the lung was diseased; it was excavated, and contained caseous foci.

The œsophageal lesions in the python come altogether in a different category. They take the form of elongated sessile swellings, the largest an inch and a half in length, and arranged with their long axes in correspondence with that of the canal. At the back of the preparation the muscular coat has been cleanly dissected away from one of the swellings, which, as thus shown, consists of a close-set series of small spherical tubercles, individually about 1·5 mm. in diameter.

Indications of the same composite structure appear in the granularity of the free surface of the larger of the projections.

On the stomach there was a similar compound mass of tubercles, six inches long, and above it, on the lower end of the œsophagus, a second about half that size; whilst a third lay on the opposite wall of the last-named canal. That connected with the stomach was at one spot deeply excavated from the inner aspect. These huge lesions, like the lesser along the course of the œsophagus, were sharply circumscribed or discontinuous with the adjacent structures, and on macroscopic section were resolvable into the same small opaque spherical tubercles, held together by connective tissue into a compound or conglomerate mass.

The anatomical disposition of these remarkable œsophageal lesions is explained by the fact that the œsophagus of Ophidia

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FIG. 32.

Portion of the œsophagus of the python described, showing enlargement of the lymph nodules from tubercular disease, without ulceration. (Slightly reduced.)

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is normally furnished with lymph nodules, or, adopting the nomenclature used in the case of the intestine, with "solitary glands."

I have examined these nodules in a sea-snake, an example of *Enhydris Hardwickii* about three feet long. In the healthy œsophagus of this snake they are conspicuous objects, and form somewhat prominent oval elevations in the axis of the canal; they have a longer diameter of 3 mm., and a shorter transverse of 1 mm. Histologically they consist of simple lymphatic tissue, and they lie immediately beneath the epithelium, which is of the columnar-celled kind as in Ophidia generally. In places capillaries are disposed immediately beneath the epithelium, or separated by the thinnest line of connective tissue. Such lymph nodules have been examined in *Vipera aspis* and in *Zamenis viridiflavus* (Oppel, 'Lehrbuch der Vergleichenden mikroskopischen Anatomie der Wirbelthiere,' 1900).

The infection of these lymph-glands is strictly parallel with the common tubercular infection of the like glands of the intestinal mucosa in man, and is to be explained by their subepithelial position, and the circumstance that the epithelium of the ophidian œsophagus is, like that of the intestine, of the columnar-celled kind, and readily allows the migration of wandering cells between its elements.

It is especially noteworthy that there is no trace of ulceration over any of the œsophageal lesions, the infection having taken place, I submit, through an intact epithelium, *i. e.* between the epithelial elements of an intact surface by means of wandering cells.

The common pigmentation of the bronchial glands is an example of the same kind, *i. e.* of the conveyance of foreign material through an intact epithelium by means of carrier cells, and makes it probable that the obsolete tubercular infection so often encountered in these glands takes place apart from a necessary primary lesion or diseased infection site.

The occurrence of such infection without surface-lesion has been established by Professor Sidney Martin in the 'Report of the Royal Commission on Tuberculosis,' 1895, Part III, Appendix, pp. 18 and 19.

Four pigs were fed upon bovine tuberculous material (meat

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and milk), and as a consequence contracted tuberculosis. Martin draws especial attention to the absence of any lesion in the alimentary track, the disease being first shown in its course from that track by an affection of the lymph-glands in connection with its different parts.

In the calf the result of experimental tubercular infection is closely paralleled by the python. Four calves, in Martin's experiments, received at one meal, mixed with their food, about one kilogramme of bovine tuberculous material. They all contracted the disease. But although a nodular lesion results, it may remain stationary without proceeding to ulceration; the intestine is affected in the form of isolated nodules as early as four weeks after feeding; the mesenteric glands become in all cases involved to a greater or less degree; from the intestinal lesion the disease in calves spreads to the lymphatic glands of the thorax, and to the lungs or pleura, or to both of these. Again, four calves received at one meal, with their food, 70 c.c. of sputum (containing a large number of tubercle bacilli) from two cases of human phthisis. These calves contracted tuberculosis, but in none was there any sign of disease, saving the nodules in the intestine.

Of the same kind is the transport of living bacteria to the organs of healthy animals during life. From the early experiments of Tiegel up to the latest by Ford, the solution of this question, presenting at the outset so delusive an exterior of simplicity, forms quite an episode in bacteriological history. The presence of bacteria in a living state, but one, so to say, of suspended animation, is a possibility not foreseen in the early stages of the inquiry.

The experiments of Tiegel[1] (who concluded that the normal viscera are *not* free of living bacteria) were made by submerging pieces of the freshly excised organs of animals in molten paraffin (110°—150° C.), which was then allowed to set. After a variable time of from four to twelve days the paraffin block was broken, and the contents examined microscopically.

The experiments of Ford[2] consisted in transferring portions of the organs of healthy animals, suddenly killed, into nutrient media, the surfaces of the pieces themselves being first sterilised

[1] 'Virch. Archiv,' vol. lx, 1874, p. 453.

[2] 'Journal of Hygiene,' vol. i, 1901.

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by cooking in the flame. Inoculations were made at the end of the first and third days, by drawing up some of the juice of the organ in a sterile glass pipette, subsequent inoculations being made until positive results were obtained, or a sufficient time had elapsed to show that the viscera were absolutely sterile. The cultures arose from those inoculations which were made from the original material on the sixth, seventh, or eighth day, or even as late as the seventeenth. The result was that in healthy domestic animals 70 per cent. showed bacteria in the internal organs provided that a sufficient time was allowed to elapse between the removal of the organs and their final examination. From the guinea-pig, *e. g.*, were isolated *Staphylococcus pyogenes aureus* and *albus*, *B. proteus*, *B. coli*, *B. subtilis*, *B. mesentericus*. The tubercle bacillus is not given in the lists. The observations of Pizzini (cited by Dr. Andrewes, 'Path. Soc. Trans.,' vol. liii, p. 310) are, therefore, worth bearing in mind in this connection. Pizzini ('Zeitschrift für klin. Med.,' 1892, xxi, p. 329) inoculated guinea-pigs with the lymphatic glands from the bodies of forty persons who had died of non-tubercular affections; tuberculosis resulted in 42 per cent. of the experiments, the bronchial glands being those which most frequently gave a positive result.

Although the lung of the python in question is tubercular, it is little diseased, and as it presents no discharging lesion the œsophageal infection cannot be attributed to auto-inoculation from this source. The tuberculosis of the alimentary canal is obviously primary, the main disease involving the stomach. From inquiries of Professor Beddard I learn that the python was two years in the Zoological Society's Gardens, and that it was fed chiefly upon ducks (kept for the purpose in the Gardens), and at times a rabbit. The bird or mammal is ingested whole, with the feathers or hair intact, and takes two or three minutes to reach the stomach, its progress along the œsophagus being easily followed. The snake was ill for two months, as told by the abnormal character of the excreta. Its last meal, a duck, was taken three weeks before death; two days later the duck was disgorged in a partially digested condition.

Acid-fast bacilli are demonstrable in sections of the œsophageal lesions, though not in large numbers; and as the unity or plurality of the tubercle bacillus is so important a question, I

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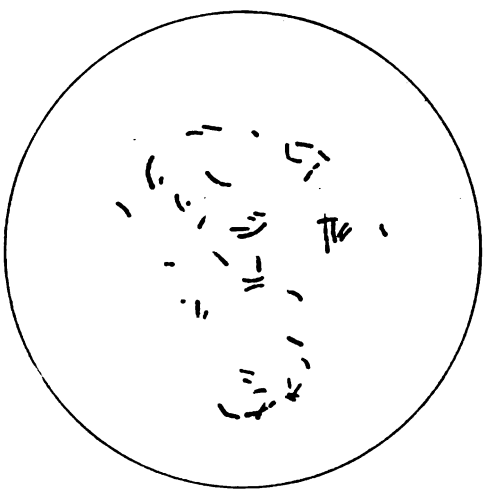
have ventured to figure an isolated group, though rather for any future value it may possibly have than for any immediate. The bacilli in the group are, some of them, stained uniformly, others typically beaded; they are in no way clubbed or branched, and most are slightly curved.

Dr. W. K. Sibley has recorded an example of spontaneous tuberculosis in a ringed snake (*Tropidonotus natrix*, var. *murorum*) in 'Virchow's Archiv,' vol. cxvi, 1889, p. 104: neither the lungs nor the heart showed any recognisable change,

FIG. 33.



An entire group of tubercle bacilli in a section of one of the diseased œsophageal lymph nodules; $\frac{1}{12}$ oil immersion, Leitz; oc. 2, tube length 170 mm. Drawn with the camera lucida. Certain of the bacilli are represented with a vanishing end to obviate any error in regard to their apparent length, which would result were they foreshortened.

nor did the pancreas; tubercular foci were present in the liver, kidneys, and sexual organs. In this case nothing was remarked concerning the œsophagus, but there were tubercular centres in the wall of the lower part of the stomach, the outer coats of which were here thickened, as well as in the serous layer of the rectum; the digestive track, moreover, showed some nodular thickening in the neighbourhood of the lower margin of the liver. The author names the condition general tuberculosis; he could not determine a local origin. Here, as in the python,

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I should myself regard the infection as having arisen in the alimentary track.

The same author records ('Path. Soc. Trans.,' vol. xliii, p. 189) two experiments in which he succeeded in producing tuberculosis in snakes. The snakes[1] were kept in glasses open at the top, the glasses being placed in a large zinc bath, the water of which was maintained at about 35° C.; they were fed regularly with frogs. The inoculations were made with a hypodermic syringe into the loose subcutaneous tissue.

In the case of the python under consideration it is to be noted that the air in the glass chamber in which the snake lived was 70° F. (21·1° C.), and that the temperature of the water in its tank was kept at 80° F. (26·6° C.).

Although Ophidia are popularly classed as "cold-blooded," the growth of the bacillus in the different cases referred to offers no difficulty. For not only was the surrounding temperature comparatively high, but, as Sir Hugh Beevor showed ('Path. Soc. Trans.,' vol. xlii, 1891, p. 344), the tubercle bacillus will grow at a temperature considerably below 37° C. The more detailed investigation of Maffucci ("Die Hühnertuberculose," 'Zeitschrift für Hygiene,' Band xi, 1892, p. 445) proved that although the best temperature for the growth of the mammalian bacillus is 37° C., the micro-organism will grow at any temperature between 30° C. and 40° C.; and that in regard to the avian bacillus, whilst the most favourable temperature lies between 30° C. and 43° C., it will nevertheless grow at the extremes of 25° C. and 45° C. Even at 20° C. sub-cultures will give a growth after the lapse of a month.

Nevertheless such data do not furnish a reliable method of differential diagnosis. It has been held that the human bacillus will not grow at a temperature below 30° C. But the successful inoculation by Moeller of the blindworm (*Anguis fragilis*) with human sputum proves that this is not a final observation, seeing that the bacillus when recovered from this "cold-blooded" lizard will grow in sub-culture at so low a degree as 22° C.

In the python the source of infection was probably avian, since the snake was fed almost exclusively upon ducks, and the keeper is a perfectly healthy man.

[1] The common English ringed snake (*Tropidonotus natrix*) and the common viper (*Pelias verus*).

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In Dr. Sibley's experiments the cultures used were obtained from the laboratory of Professor Crookshank, and the source was human sputum, though Professor Crookshank tells me he cannot be sure whether the culture was raised directly from the sputum or through the intervention of the guinea-pig.

June 17th, 1902.

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PART III.

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